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ORIGINAL ARTICLE

Blood component requirements in liver transplantation: effect of 2 thromboelastometry-guided strategies for bolus fibrinogen infusion—the TROMBOFIB randomized trial

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Abstract

Background: A low plasma fibrinogen level influences blood component transfusion. Thromboelastometry provides clinical guidance for fibrinogen replacement in liver transplantation (LT).

Objectives: We hypothesized that infusions of fibrinogen concentrate to reach an $A10_{FIBTEM}$ value of 11 mm during LT could reduce red blood cell (RBC) and other component and fluid requirements in comparison to standard care.

Methods: This randomized, blinded, multicenter trial in 3 hospitals enrolled 189 LT-scheduled patients allocated to an intervention target ($A10_{FIBTEM}$, 11 mm) or a standard target ($A10_{FIBTEM}$, 8 mm); 176 patients underwent LT with fibrinogen replacement. Data were analyzed by intention-to-treat (intervention group, 91; control group, 85). Blood was extracted, and fibrinogen kits were prepared to bring each patient's fibrinogen level to the assigned target at the start of LT, after portal vein clamping, and after graft reperfusion. The main outcome was the proportion of patients requiring RBC transfusion during LT or within 24 hours.

Results: The proportion of patients requiring RBCs did not differ between the groups: intervention, 74.7% (95% CI, 65.5%-83.3%); control, 72.9% (95% CI, 62.2%-82.0%); absolute difference, 1.8% (95% CI, −11.1% to 14.78%) (P = .922). Thrombotic events occurred in 4% of the patients in both groups; reoperation and retransplantation rates and mortality did not differ. Nearly 70% of the patients in both groups required fibrinogen concentrate to reach the target. Using an 11-mm $A10_{FIBTEM}$ target increased the maximum clot firmness without affecting safety. However, this change provided no clinical benefits.

Conclusion: The similar low plasma fibrinogen concentrations could explain the lack of significant between-group outcomes.

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KEYWORDS
blood component transfusion, fibrinogen, hemostasis, liver transplantation, thromboelastography

1 | INTRODUCTION

Hemostatic and coagulation disorders related to severe liver disease are known to cause massive bleeding in liver transplantation (LT), and packed red blood cells (RBCs) are commonly transfused. For example, in a recent large case series, 19% of patients received more than 6 units [1], an amount approaching massive transfusion. Although the altered hemostasis of end-stage liver disease is multifactorial, a low plasma fibrinogen level plays a part and influences blood component transfusion [2,3]. Fluid resuscitation after surgical bleeding may aggravate the problem by decreasing the concentration of fibrinogen [4].

In a previous randomized, multicenter, double-blinded, placebo controlled trial of a single dose of preemptive fibrinogen concentrate administered just before surgery, our group found that the intervention did not influence transfusion requirements [5]. That strategy gave a mean increase in the fibrinogen level of only 0.32 g/L per gram of the concentrate infused and failed to maintain average levels within the targeted range over the course of the procedure. Therefore, it seemed that further study of a strategy to maintain plasma fibrinogen levels throughout the course of an LT procedure would be required.

Fibrinogen infusion guided by thromboelastometry is strongly recommended as a way to tailor management [6–10]. There is a correlation between plasma concentration and maximum clot firmness (MCF), demonstrated by thromboelastometry for fibrin function (FIBTEM), and an MCF of 6 mm has been reported to predict a plasma concentration of 1 g/L in children undergoing LT [11]. We found that a value of 8 mm for the MCF amplitude at 10 minutes by FIBTEM ($A10_{FIBTEM}$) predicts blood product requirements and hypothesized that $A10_{FIBTEM}$ might also provide clinical guidance for fibrinogen replacement in LT [12]. We found no studies exploring the utility of values higher than 8 mm in this scenario and currently use that target for guidance in clinical practice.

For this randomized trial, we hypothesized that, assuming comparable patient risk factors for RBC transfusion, bolus infusions of fibrinogen concentrate to reach and then maintain a high $A10_{FIBTEM}$ value of 11 mm at critical phases of LT could reduce RBC and other blood product requirements more effectively than our standard management approach of maintaining an $A10_{FIBTEM}$ of 8 mm.

Essentials

- Low plasma fibrinogen influences blood component requirements in liver transplantation.
- Patients were randomized to fibrinogen replacement guided by thromboelastometric readings of 11 or 8 mm.
- The proportion of patients requiring red blood cell transfusion did not differ between the groups.
- Similar plasma fibrinogen concentrations in both groups could explain the lack of significant differences.

2 | MATERIALS AND METHODS

2.1 | Study design

This randomized, blinded, multicenter trial was conducted in 3 teaching hospitals in Spain after approval was obtained from the institutional review board (IRB) of the lead hospital (University Hospital of Bellvitge, approval number AC 033/18), the IRBs of the other participating centers, and the Spanish Ministry of Health and Science. The trial was registered in the European Clinical Trials Database (EudraCT 2018-002510-13) and at ClinicalTrials.gov (NCT01539057).

2.2 | Patients

Adults aged 18 to 80 years scheduled for LT were eligible. From August 2, 2019, to November 2, 2021, we assessed patients for eligibility. The exclusion criteria were as follows: a preoperative hemoglobin level of >130 g/L; a history of allergic reaction to fibrinogen concentrate; receiving aspirin, warfarin, or other anticoagulation therapy; a known history of thromboembolic events in the last 30 days; known or suspected pregnancy; retransplantation in a patient previously randomized in this trial; and known presence of a congenital bleeding disorder. We also excluded patients whose indication for LT was familial polyneuropathy, who were receiving a graft from living donors, because of variability in surgical techniques. Similarly, patients undergoing LT for reasons associated with a high risk of hypercoagulation (acute liver failure or complete portal vein thrombosis) were excluded.

The trial was explained to all patients, who were also given printed information. Patients were enrolled if they gave their written informed consent. Recruitment took place at 2 university teaching hospitals in Barcelona (University Hospital of Bellvitge and the Hospital Clinic of Barcelona) and 1 in Bilbao (University Hospital of Cruces). No center could enroll more than 40% of the patients.

2.3 | Donor procurement, anesthesia, and surgical management

Liver allografts from brain-dead organ donors were preserved in University of Wisconsin solution. Organ recovery from controlled cardiac-death donors met the acceptance criteria established by the Spanish Liver Transplantation Society [13]. Normothermic regional perfusion

was performed in the recovery of organs from nonliving donors in all centers. In brief, a bolus of heparin was administered and cannulation was established before withdrawal of ventilatory support and after obtaining consent. After cannulation of 1 femoral artery, the contralateral femoral artery was cannulated with a deflated aortic occlusion balloon catheter, which was advanced into the supraceliac aorta under radiologic control. With cannulation complete, the endotracheal tube was disconnected from the ventilator, marking the start of warm ischemia. Death was declared after 5 minutes of complete absence of spontaneous circulation and respiration. The aortic occlusion balloon was then inflated, the normothermic regional perfusion circuit was opened, and *in situ* cold perfusion with preservation fluid was started.

The anesthesia protocols were monitored to ensure consistency and compliance across all of the research centers. All patients were placed on a convective air blanket (WarmTouch, Mallincrod Medical). Oxygen was given for 5 minutes before standard anesthesia management was started. Arterial and central venous cannulas were placed, and crystalloid fluid replacement (2 mL/kg/h) was performed to maintain volume; 8 g of albumin 20% was infused per liter of ascites evacuated. Sodium bicarbonate (1/6 M) was administered to maintain a pH of 7.3. Intravenous calcium was administered to keep the plasma calcium ion concentration within the reference ranges stipulated by each hospital's laboratory. Normothermia was maintained. Vena cava preservation was attempted in all patients. The surgical technique was recorded in the patient's electronic case record form (CRF).

Before reperfusion of the graft, it was flushed with 1000 mL of Hartmann's solution at 38 °C to remove air and detritus from the wall of the graft's inferior vena cava. Next, the distal end of the donor's vena cava was closed with a vascular stapler. Vasoconstrictor drugs were administered to compensate for reperfusion syndrome. At the end of surgery, all patients remained mechanically ventilated on transfer to a surgical intensive care unit.

2.4 | Intraoperative and postoperative transfusion management

The protocols for blood component transfusions were monitored to ensure consistency and compliance across the 3 hospitals. The infusion criteria were as follows: RBCs to maintain a hemoglobin level of >80 g/L, platelet concentrates if a count fell below 30 000/mm^3, and intravenous tranexamic acid boluses of 500 mg if fibrinolysis (ie, >15% lysis at 60 minutes) was detected by FIBTEM. Cell saver devices were not used. Hemostatic surgical management followed a standard protocol. In case of massive bleeding (>150 mL/min), we also monitored MCF by extrinsic thromboelastometry for fibrin tissue factor activation (EXTEM) ($A10_{EXTEM}$). If we detected a value of <15 mm or a clotting time of >300 seconds by FIBTEM, we simultaneously transfused 4 units of RBCs, 1 g of tranexamic acid, 2 g of fibrinogen concentrate, 1 unit of apheresis platelets, and 15 mL/kg of fresh frozen plasma.

Thromboelastometry was performed with a ROTEM device (Tem International GmbH) at all of the centers. Fibrinogen plasma concentration was measured fully by the automated Clauss method at each center.

2.5 | Randomization and masking

All trial data were collected and anonymously stored in each patient's electronic CRF; each patient was assigned a unique study number and a unique randomization number. The randomization sequence was created using a computer-generated random list, which was then stratified according to whether the baseline hemoglobin concentration was <95 g/L or not and by center (1:1 ratio, in blocks of multiples of 2 units). Just before surgery, patients were allocated to 1 of 2 parallel groups to receive human fibrinogen concentrate (1 g in 50 mL of water, RiaSTAP, CSL Behring) according to whether an $A10_{FIBTEM}$ value of 8 mm or 11 mm would guide fibrinogen replacement.

The anesthesia nurse was responsible for obtaining blood samples for thromboelastometry readings and preparing the fibrinogen infusion kit appropriate for each patient's group assignment. The nurse extracted blood samples for the analysis of $A10_{FIBTEM}$ and $A10_{EXTEM}$ at successive stages of LT as follows: T1, before anesthesia induction; T2, 10 minutes after portal clamp; T3, 10 minutes after graft reperfusion; and T4, end of surgery. At T1, the nurse prepared a fibrinogen kit to bring the patient's $A10_{FIBTEM}$ value to 11 mm (intervention group) or 8 mm (control group). At T2 and T3, the nurse again prepared a kit to bring the $A10_{FIBTEM}$ value to the level assigned to each patient. At T4, the $A10_{FIBTEM}$ value was recorded in the CRF. To calculate the dose for an intervention-group patient, the nurse subtracted the $A10_{FIBTEM}$ value from 11 mm and multiplied by 1.1 g (ie, [11 mm − $A10_{FIBTEM}$] × 1.1 g), according to the mean increase of 0.32 g/L per gram of concentrate infused, which was determined in our previous study.[5] For the control group, the formula was as follows: (8 mm − $A10_{FIBTEM}$) × 1.1 g. Once a kit was prepared, the nurse brought it into the operating room. The surgeon and anesthetist remained masked, as did patient and outcome assessors.

A data quality monitoring procedure was established to ensure that all the aforementioned fibrinogen level checks were performed at the stipulated times in each hospital and that the results were recorded and reported in accordance with the trial protocol and good clinical practice. The fibrinogen and blood component amounts provided by the pharmacy and blood bank were also recorded and checked against the amounts used according to the CRFs. Members of the IRBs and the public health funding agency had access to patient data throughout the study period. Outcome assessments were performed regularly at preset follow-up intervals as patients were included in the trial. The protocol, informed consent sheets, statistical analysis plan, CRFs, and datasets were stored by the IRB of the lead hospital and the IDIBELL Foundation.

2.6 | Outcomes

The primary outcome measures were the proportion of patients requiring RBC transfusion during LT and within the next 24 hours in each group and the number of units required.

The secondary outcome measures included requirements in each group for the infusion of apheresis platelets, fresh frozen plasma and other blood components, and tranexamic acid in each group during LT

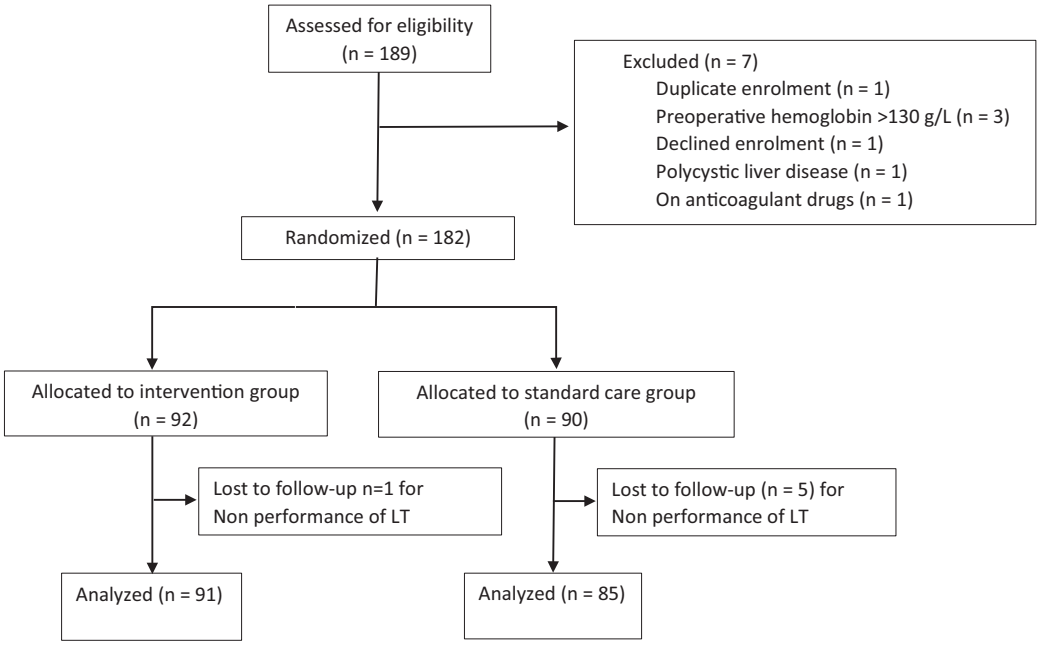

FIGURE 1 Flowchart showing patient enrolment, exclusions, and losses for nonperformance of surgery. LT, liver transplantation.

and within the next 24 hours. The amounts administered were also recorded. During LT and for the following 90 days, we also evaluated the incidence of acute kidney injury according to the scale recommended in guidelines [14]. Other outcomes that were analyzed up to 90 days were the duration of mechanical ventilation in hours in each group, thrombotic events in the graft or legs (assessed via Doppler ultrasound), and thrombotic events in the lung (by computed tomography). Reoperations for any cause, retransplantations, and deaths were also recorded.

All adverse events related to fibrinogen administration were recorded in the CRF, and the principal investigator (A.S.) was notified immediately. The data monitoring committee also reviewed all adverse events, and an annual safety report was sent to the Spanish Agency for Drugs and Medical Products and the IRBs that approved the protocol.

2.7 | Statistical analysis

We estimated a sample size of 176 patients (88 per group); the statistical power would be 80% for detecting an absolute reduction of 30% in the proportion of patients requiring transfusion. We assumed that 80% of patients would receive RBCs in the standard-care arm, a 2-sided α level of 0.0294 adjusted for the interim analysis sample size (overall two-sided α, 5%), and a 10% drop-out rate. The interim analysis by the independent data monitoring committee was planned to take place when data were available for 90 patients in case early termination was necessary because the null hypothesis was rejected using the Pocock group's sequential method or because of futility in using a conditional power cut-off point of 30%.

Intention-to-treat (ITT) analysis was used to assess the main endpoint, secondary endpoints, and safety variables. Thus, all randomized patients who underwent LT as scheduled were included, regardless of protocol adherence, to control for bias. Only patients who did not undergo the LT procedure were excluded from the analysis. Patient characteristics and hemoglobin, coagulation, and fibrinogen baseline profiles were calculated according to the nature of each variable. The absolute between-group difference (and 95% CI) in the proportion of patients requiring RBC transfusion during LT or within 24 hours (the primary outcome) was also calculated. To compare primary and secondary outcomes according to group assignment, parametric or nonparametric tests were used for continuous variables (according to normality or nonnormality of distribution). For categorical variables, chi-square tests or Fisher exact tests were used. The relative risk (RR) and its 95% CI were also calculated.

We compared median (IQR) plasma fibrinogen levels and ExTem and FibTem MCF measurements during LT between groups using the Kruskall-Wallis test. We also compared the changes in these variables before and after infusions at the time of each measurement corresponding to an LT phase using this test. All criteria for the application of the test were checked. The statistical package used for the analyses was R, version 4.1.0 (2021-05-18) for Windows (R Foundation for Statistical Computing) [15].

3 | RESULTS

A total of 189 patients were recruited; 7 patients were excluded before randomization for various reasons, leaving 182 to be randomized (Figure 1). Ninety-two patients were initially assigned to the intervention group ($A10_{FibTem}$ target, 11 mm) and 90 patients were assigned to the control group (standard-care target, 8 mm). However, 5 patients assigned to the intervention group and 1 patient assigned to the control group were excluded owing to cancelation of their LT

TABLE 1 Patient characteristics and hemoglobin, coagulation, and fibrinogen baseline values.

Patients	Intervention group FIBTEM ≥ 11 mm (n = 91)	Control group FIBTEM ≥ 8 mm (n = 85)
Age (y)	58 (8.83)	58.7 (8.43)
Male	80.2%	77.6%
Female	19.8%	22.4%
Weight (kg)	78.4 (14.3)	77.9 (15.9)
Height (cm)	169 (8.7)	170 (9.19)
BMI (kg/m^2)	27.4 (4.39)	7.1 (5.0)
Alcoholic cirrhosis	54.9%	61.2%
NASH	8.7%	9.4%
Tumor	9.9%	9.4%
Other	26.5%	20%
Prior abdominal surgery	28.6%	36.5%
Diabetes	35%	30.6%
Partial portal thrombosis	9.89%	3.53%
Altered echocardiogram	13.2%	20%
Pulmonary disease	18.7%	16.5%
Ascites	46%	55.3%
Sodium (mEqu/L)	134 (5.4)	135 (5.24)
Creatinine (mg/dL)	1.06 (0.76)	1.13 (0.49)
MELD score	18.5 (6.7)	18.8 (7)
Child-Pugh score		
A	15.3%	15.3%
B	37.4%	30.4%
C	47.2%	54.1%
Hemoglobin (g/L)	94 (84.5-110)	91 (83-108)
<95 g/L	61.5%	60%
≥95 g/L	38.5%	40%
Platelet count (10^3/mm^3)	75.0 (52.5-98.5)	71.5 (52.8-101)
PTT	1.23 (1.06-1.36)	1.20 (1.04-1.38)
INR	1.55 (1.34-1.77)	1.55 (1.33-1.92)
Fibrinogen (g/L)	2.00 (1.35-3.05)	1.92 (1.30-3.02)
EXTEM		
Coagulation time (s)	64 (58-76)	66 (60-74.2)
MCF (mm)	51 (42.5-60)	50 (43-59)
Lysis (%)	0 (0-0)	0 (0-0)
FIBTEM MCF (mm)	11 (7-17)	12 (6-18)

Data are presented as mean (SD), median (IQR), or percentage.

BMI, body mass index; EXTEM, extrinsic thromboelastometry for fibrin tissue factor activation; FIBTEM, thromboelastometry for fibrin tissue factor activation and platelet inhibition; INR, international normalized ratio; MCF, maximum clot firmness; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PTT, partial thromboplastin ratio.

procedures and were, therefore, never treated with replacement fibrinogen concentrate. Two major protocol violations occurred in the intervention group when data quality monitoring detected that the wrong fibrinogen replacement dose formula had been used for kit preparation; these patients were included in the analysis (ITT). The independent data monitoring committee released their report on March 2, 2021. Their analysis of both the primary endpoint and secondary endpoints using data for the first 90 patients enrolled indicated that the trial should continue.

No significant differences emerged in patient baseline characteristics between the 2 groups, including hemoglobin stratification (Table 1). Similarly, patient characteristics were distributed similarly across the 3 centers, with no significant differences. However, brain-dead donor grafts were used more often in the intervention group (69 patients [75.8%] vs 51 [60.0%] in the control group, P = .037).

Platelet counts, plasma fibrinogen and hemoglobin levels at the 4 measurement times, and EXTEM and FIBTEM MCF measurements are shown in Table 2 and illustrated in Figure 2. Baseline (T1) values of plasma fibrinogen of <1 g/L and MCF of <6 mm were detected in 8 (8.9%) patients and 23(25.3%) patients, respectively, in the intervention group; the same findings were recorded in 7 (8.4%) patients and 24(28.9%) patients, respectively, in the control group. The amounts of fibrinogen concentrate administered were similar, and the highest amounts of fibrinogen were given after graft reperfusion (T3) in both groups. Patients in the intervention group required significantly larger infusions of fibrinogen concentrate (median, 5 to 7 g, vs 4 to 5 g in the control group at the different times) to reach the target. In spite of fibrinogen bolus doses during LT in the majority of patients in both groups, plasma fibrinogen concentrations remained <1g/L in 2 (2.25%) patients at T2, in 3 (3.33%) patients at T3, and in no patients at T4 in the intervention group (vs in 2 [2.41%] patients at T2, 10 [11.9%] patients at T3, and 5 [6.02%] patients at T4 in the control group). Platelet counts and EXTEM MCF values increased during LT in both groups. In contrast, hemoglobin levels, which were lowest at reperfusion (T3), decreased in both groups and remained lower than baseline at the end of LT.

The ITT analysis revealed no significant between-group differences in the percentage of patients requiring RBC transfusions during LT and within the next 24 hours (primary outcome): intervention group, 74.7% (95% CI, 65.5%-83.3%); control group, 72.9% (95% CI, 62.2%-82.0%). The absolute difference was 1.8%. (95% CI, −11.1 to 14.78) (P = .0922). In addition, the number of RBC units required did not differ. The RR for RBC transfusion overall was 0.95 (95% CI, 0.77-1.18) (Table 3). Although a slightly higher percentage of patients in the intervention group required massive RBC transfusions (>6 units), the difference was not significant. All activations of the massive bleeding (>150 mL/min) protocol happened at graft reperfusion (T3). This event occurred in 10 patients in the intervention group and 9 patients in the control group (around 10% of the series overall). Five (5.49%) patients in the intervention group and 10 (11.8%) patients in the control group required apheresis platelets during liver resection (T2). Even so, the need for fresh frozen plasma, platelets, and tranexamic acid infusion did not differ between the groups (Table 3).

TABLE 2 Hemoglobin, platelet count, and fibrinogen values and extrinsic thromboelastometry for fibrin tissue factor activation and thromboelastometry for fibrin tissue factor activation and platelet inhibition maximum clot firmness measurements at each stage of liver transplantation.

Patients	Intervention group FIBTEM ≥ 11 mm (n = 91)	Control group FIBTEM ≥ 8 mm (n = 85)	*P* value[c,d]
Hemoglobin (g/L)			
T1	94.0 (84.5 to 110.0)	91.0 (83.0 to 108.0)	.484
T2	94.0 (82.5 to 110.0)	93.0 (80.0 to 109.0)	.532
T3	91.0 (76.5 to 100.0)	86.0 (76.0 to 101.0)	.644
T4	89.0 (81.5 to 96.5)	88.0 (83.0 to 100.0)	.908
Platelet counts (10^3/mm^3)			
T1	75 (52.5 to 98.5)	71 5 (52.8 to 101)	.774
T2	88 (65.5 to 117)	97 (72 to 138)	.290
T3	80 (62 to 126)	87 (64 to 120)	.565
T4	91 (67 to 133)	94 (67 to 126)	.613
Plasma fibrinogen (g/L)			
T1	2 (1.35 to 3.05)	1.92 (1.3 to 3.02)	.833
T2	2.24 (1.62 to 2.87)	2.03 (1.40 to 2.66)	.113
T3	1.88 (1.43 to 2.34)	1.62 (1.36 to 2.20)	.077
T4	1.97 (1.5 to 2.48)	1.69 (1.35 to 2.05)	.010
EXTEM MCF (mm)			
T1	51 (42.5 to 60)	50 (43 to 59)	.598
T2	55.5 (50 to 62.8)	54 (48 to 60.9)	.238
T3	54 (51 to 59)	52 (49 to 60)	.169
T4	56 (51 to 61.5)	53 (49 to 60)	.065
FIBTEM MCF (mm)			
T1	11 (7 to 17)	12 (6 to 18)	.793
T2	12 (10 to 16)	10 (8 to 15)	.002
T3	12 (10 to 14)	10 (8 to 13)	.005
T4	14 (12 to 16)	10.5 (8 to 15)	.001
Fibrinogen administered (g)			
T1 to T2[a,b]	51.6%; 5 (2 to 6.5)	41.2%; 4 (2 to 5)	.215[c]; .341[d]
T2 to T3[a,b]	64.8%; 5 (3 to 7)	52.9%; 4 (3 to 7)	.147[c]; .305[d]
T3 to T4[a,b]	70.3%; 7 (4 to 10)	64.7%; 5 (4 to 7)	.525[c]; .033[d]
Differences after fibrinogen boluses			
EXTEM MCF (mm)			
T1 vs T2	5.1 (3.6 to 6.5)	4.9 (3.2 to 6.6)	.407
T1 vs T3	2.8 (0.7 to 4.8)	2.1 (−0.5 to 4.6)	.354
T1 vs T4	5.5 (3.5 to 7.4)	4.8 (2.2 to 7.5)	.323
Plasma fibrinogen (g/L)			
T1 vs T2	0.1 (−0.1 to −0.2)	0.1 (−0.2 to −0)	.109
T1 vs T3	−0.3 (−0.5 to −0.1)	−0.5 (−0.6 to −0.3)	.518
T1 vs T4	−0.3 (−0.5 to −0.1)	0.5 (−0.7 to −0.3)	.155

(Continues)

TABLE 2 (Continued)

Patients	Intervention group FIBTEM ≥ 11 mm (n = 91)	Control group FIBTEM ≥ 8 mm (n = 85)	*P* value[c,d]
FIBTEM MCF (mm)			
T1 vs T2	1.2 (−2.5 to 2.6)	−0.1 (−1.42 to 1.2)	.020
T1 vs T3	−0.5 (−1.7 to 0.7)	−1.5 (−2.5 to −0.5)	.122
T1 vs T4	1.5 (0.1 to 2.8)	−1 (−2.6 to 0.6)	.001

Data are presented as median (IQR) and percentage.

EXTEM, extrinsic thromboelastometry for fibrin tissue factor activation; FIBTEM, thromboelastometry for fibrin tissue factor activation and platelet inhibition; MCF, maximum clot firmness; T1, baseline; T2, 10 minutes after portal clamp; T3, 10 minutes after reperfusion of the liver graft; T4, end of the procedure.

[a] The percentage refers to patients who received fibrinogen concentrate.

[b] The median (IQR) refers to the amount of fibrinogen concentrate infused in grams.

[c] The *P* value referring to percentage comparison.

[d] The *P* value referring to median comparison.

Similarly, there were no between-group differences in the rates of LT-related adverse events (Table 3). Although hepatic artery, portal vein, and other systemic thromboses were present in 4 patients in each group, 3 of the 8 patients (2 in the intervention group and 1 in the control group) had received no fibrinogen concentrate infusions. Acute renal failure was present in similar percentages of patients in both groups. Furthermore, the median hours of postoperative mechanical ventilation did not differ between the groups.

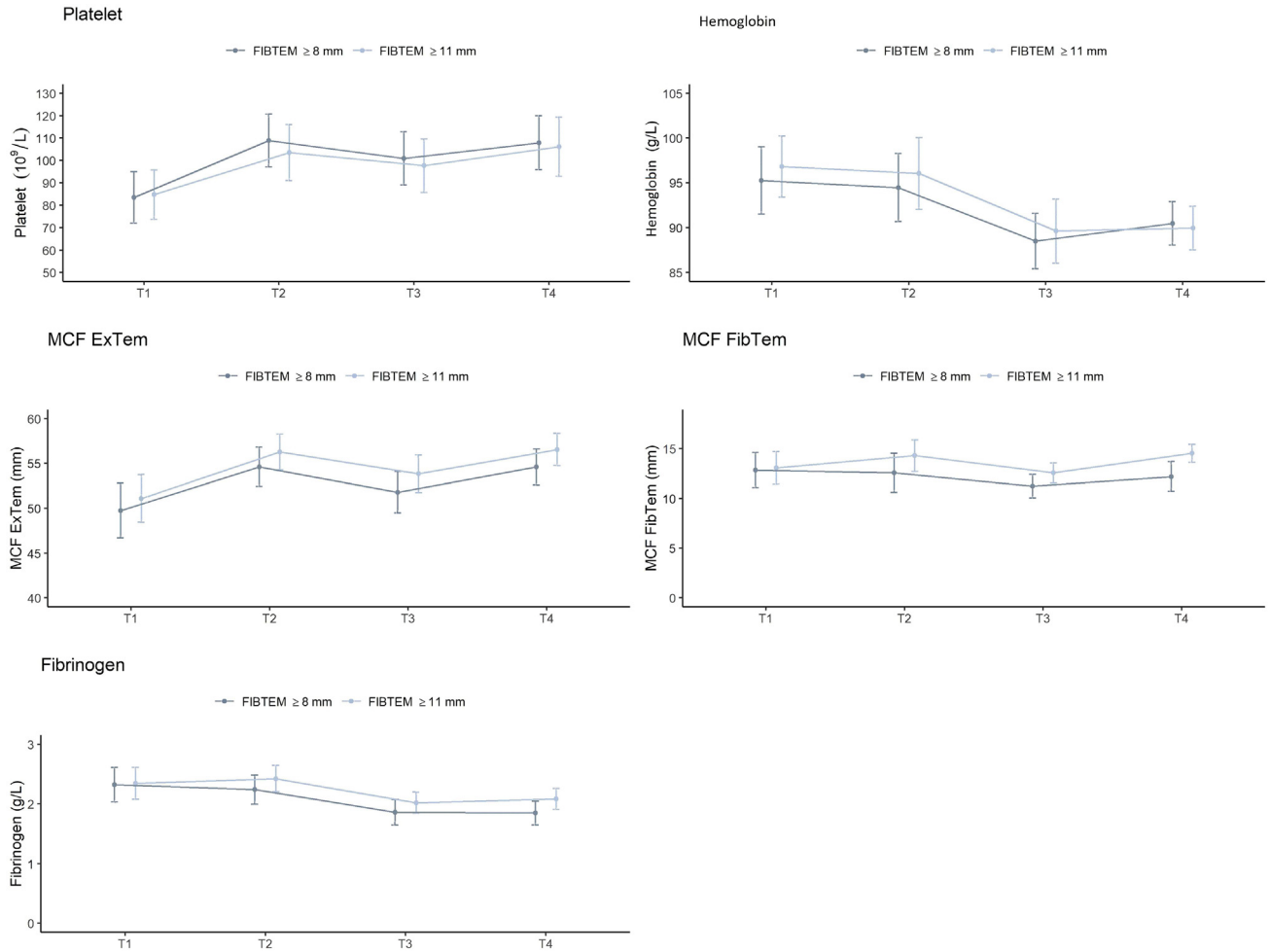

FIGURE 2 Graphs illustrating how similar platelet and hemoglobin requirements, measurements of maximum clot firmness (MCF) by extrinsic thromboelastometry for fibrin tissue factor activation (EXTEM) and thromboelastometry for fibrin tissue factor activation and platelet inhibition (FIBTEM), and fibrinogen plasma concentrations were in the intervention group (blue lines) and control group (black lines).

TABLE 3 Red blood cell, blood component and fluid therapy requirements, surgical events, and outcomes.

Patients	Intervention group FIBTEM ≥ 11 mm (n = 91)	Control group FIBTEM ≥ 8 mm (n = 85)	*P* value[d,e]	RR value
Length of surgery (min)	380 (302 to 1422)	390 (305 to 1457)	-[d]; .916[e]	-
Cold ischemia (min)	380 (279 to 437)	365 (286 to 400)	-[d]; .986[e]	-
Warm ischemia (min)	40 (26 to 53)	37 (29 to 52)	-[d]; .956[e]	-
Reperfusion syndrome	44%	49.4%	.566	0.89 (0.64 to 1.22)
During LT				
RBCs,[a,b] (units)	64.8%; 3 (2 to 6)	68.2%; 3 (2 to 4.75)	.75[d]; .32[e]	0.95 (0.77 to 1.18)
FFP,[a,b] (units)	11.1%; 2 (2 to 3.5)	14.1%; 2 (2 to 4)	.90[d]; .90[e]	0.78 (0.35 to 1.71)
Platelets,[a,b] (units)	9.89%; 1 (1 to 1)	17.6%; 1 (1 to 2)	.21[d]; .31[e]	0.56 (0.25 to 1.19)
Tranexamic acid (n)	36 (39.6%)	31 (36.5%)	.79	1.08 (0.7 to 1.6)
During and 24 h after surgery				
RBCs[a,b] (units)	74.7%; 4 (2 to 7.25)	72.9%; 3.5 (2 to 5)	.72[d]; .74[e]	1.02 (0.86 to 1.23)
>6 units RBCs (n)	11 (12.1%)	5 (5.9%)	.243	2.05 (0.75 to 6.3)
>10 units RBCs (n)	4 (4.40%)	2 (2.35%)	.683	1.87 (0.37 to 13.23)
FFP[a,b] (units)	18.7%; 2 (2 to 4)	17.9%; 2 (2 to 4)	.91[d]; 1[e]	1.05 (0.56 to −1.99)
Platelets[a,b] (mL)	20.9; 1 (1 to 2)	25.9%; 2 (1 to 3)	.54[d]; .078[e]	0.81 (0.46 to 1.38)
Fibrinogen[a,b] (g)	72.5%; 7.5 (4 to 10)	65.9%; 6 (4 to 9)	.429[d]; .153[e]	1.1 (0.9 to 1.35)
Fluid therapy[c] (mL)	5334 (4131 to 7184)	5198 (4200 to 7099)	.88	-
Reoperations (n)	10 (11%)	11 (12.9%)	.868	0.85 (0.37 to 1.91)
Thrombotic complications (n)	4 (4.40%)	4 (4.71%)	1.0	0.93 (0.23 to 3.84)
Acute renal failure (n)	12 (13.2%)	15 (17.6%)	.541	0.75 (0.36 to 1.5)
Mechanic ventilation (hours)	13 (9 to 19.5)	11 (9 to 15.8)	.118	-
Retransplantation or death (n)	1 (1.1%)	4 (4.71%)	.198	0.23 (0.01 to 1.54)

Data are presented as n (%) of patients, followed by median (IQR) where shown.

FFP, fresh frozen plasma; LT, liver transplantation; RBCs, red blood cells; RR, relative risk; T1, baseline; T2, 10 min after portal clamp; T3, 10 min after reperfusion of the liver graft; T4, end of procedure.

[a] The percentage refers to patients who received RBC.

[b] The median (IQR) value refers to the amount of fluid infused.

[c] Fluid therapy refers to nonblood products (colloids, crystalloids).

[d] *P* value referring to percentage comparison.

[e] *P* value referring to median comparison.

4 | DISCUSSION

Bolus fibrinogen infusions to maintain an $A10_{FIBTEM}$ of 11 mm during LT were associated with intraoperative and 24-hour RBC transfusion and fresh frozen plasma and platelet requirements, which were similar to those in the standard-practice group (target $A10_{FIBTEM}$ reading, 8 mm). Blood product infusions were needed the most after graft reperfusion, when bleeding and hemodilution led to a clear decrease in hemoglobin levels and instability. These events, even though temporary, contributed to high RBC transfusion requirements in both groups.

Nearly 73% of our patients in both groups required RBC correction during LT and in the following 24 hours. This figure is consistent with the low baseline hemoglobin concentrations of 95 g/L or less in approximately 60% of patients in both groups, indicating a high risk for RBC transfusion. Hemoglobin levels further decreased during LT, as indicated by a median concentration of approximately 88 g/L in both groups at the end of surgery. A post hoc analysis of our data showed that nearly all patients with baseline hemoglobin levels lower than 110 g/L required RBCs (92.85% in the intervention group and 94.34% in the control group). In contrast, only approximately 40% of patients with hemoglobin concentrations higher than 110 g/L required transfusions.

In parallel, we observed that the plasma fibrinogen level and MCF FIBTEM values decreased in both groups, indicating consumption of fibrinogen in spite of bolus infusions that met the randomly assigned $A10_{FIBTEM}$ targets. The more pronounced decrease after graft reperfusion is probably the effect of hemodilution and is expected at this stage of LT. As a result, nearly 70% of our patients in both groups

required fibrinogen replacement at this time. Even so, MCF FIBTEM values were significantly different between the groups after the first fibrinogen infusion (during liver resection), during reperfusion of the graft, and at the end of the procedure. There were no inconsistencies between the planned fibrinogen replacement targets and the actual MCF results achieved during the procedure. On the contrary, both groups showed decreases in plasma fibrinogen in all phases of LT, even though 10 patients in the control group (11.9%) reached a plasma fibrinogen concentration of 1g/L or lower at reperfusion and only 3 patients (3.33%) did so in the intervention group. A lack of correlation between plasma fibrinogen concentration and FIBTEM values after reperfusion has been reported previously [12] and could explain why the differences in MCF FIBTEM findings between the groups did not translate to higher plasma fibrinogen concentrations. The randomization sequence ensured that variations affected both groups in all centers. Therefore, the coefficient of variation for fibrinogen measurements by the Clauss method used would have influenced the plasma fibrinogen concentration values similarly across the groups and centers. Functional fibrinogen can also be calculated automatically on the basis of clot firmness by eliminating the platelet contribution in viscoelastic tests; however, in bleeding patients during surgery and after graft reperfusion, the calculated values seem to be overestimated compared with the values measured using the conventional Clauss method [7]. The similar low plasma fibrinogen concentrations we observed could explain the lack of significant between-group outcomes.

Few patients required fresh frozen plasma and apheresis platelets, consistent with successful management of blood component infusion guided by thromboelastometry [9]. We also found that MCF measured by EXTEM stayed above the baseline during the whole procedure. The intervention group had higher median EXTEM MCF readings in all phases of LT, even when a lower platelet count was registered. The higher MCF values could conceivably be explained by the greater amount of fibrinogen concentrate these patients were given to meet the 11-mm $A10_{FIBTEM}$ target. We noted a slight tendency to administer more apheresis platelets in the control group during liver resection, a time at which increased bleeding is expected; however, the difference was not significant.

Continuous blood oozing, a result of fibrinolysis that can be detected by thromboelastometry and requires tranexamic acid administration, was also similar in both groups, consistent with previous reports [5,9]. However, a post hoc analysis of the data showed that, after adjustment for the Model for End-Stage Liver Disease score, the RRs for tranexamic acid infusion in relation to baseline $A10_{FIBTEM}$ and baseline fibrinogen concentration were 0.77 (95% CI, 0.60-0.97) and 0.59 (95% CI, 0.43-0.78), respectively, indicating the advantage of correcting low $A10_{FIBTEM}$ and fibrinogen concentration values.

Significantly fewer patients in the intervention group received grafts from controlled cardiac-death donors, which might have contributed to bias in our results. However, a recent study of a consecutive retrospective series demonstrated the noninferiority of cardiac-death donation with respect to RBC transfusion requirements and the occurrence of reperfusion syndrome [16]. Liver graft quality has also been linked to ischemia times [17]. However, ischemia times were similar in our study groups and would not have influenced the interpretation of results.

Fibrinogen supplementation to maintain the $A10_{FIBTEM}$ at 11 mm increased the substrate available for fibrin generation over that provided by our hospitals' standard use of an 8-mm target, potentially increasing the risk of vascular thrombosis in the intervention group. However, we did not observe more thromboembolic events in the intervention group, supporting the safety of the 11-mm target. The proportion of such events stayed at approximately 4% in both groups, consistent with previous studies [5,8] and a large surveillance program [18].

The main principles of patient blood management in surgical settings are to minimize blood loss and optimize blood hemostasis, as we attempted in our trial. We did not take steps to improve the hemoglobin concentration before surgery. Hemoglobin optimization in patients with liver disease is clinically challenging. However, given the impact of baseline hemoglobin concentration on RBC requirements that we and others have observed, this principle merits attention in future research.

Our study is the only completed randomized trial to assess the efficacy of a fibrinogen replacement strategy carried out during the entire LT procedure. The strengths of our trial include the participation of 3 high-volume LT hospitals, on-time recruitment of patients even in the context of the COVID-19 pandemic, high adherence to protocols, and monitoring of data quality by an independent committee. A limitation of our trial was that the fibrinogen infusion kits were not prepared and masked in the pharmacy departments of our participating hospitals. However, this was a necessary aspect of providing fibrinogen replacement on the basis of the $A10_{FIBTEM}$ values just before and at 2 points during LT. To maintain masking in our study, the surgical nurse responsible for reading the $A10_{FIBTEM}$ values and preparing the kits worked in an adjacent room away from the operating area, where the surgeon and anesthetist were present. Thus, these caregivers could remain blinded to group assignment during LT and in the next 24 hours as well as during data analysis. In addition, there were no inconsistencies between the targets guiding fibrinogen replacement and the actual MCF values and plasma fibrinogen concentrations achieved during the procedure.

Our study confirms that using an $A10_{FIBTEM}$ target of 11 mm to guide fibrinogen replacement was not superior to the standard 8-mm target in terms of reducing RBC requirements. Secondarily, we also confirmed the marked and similar loss of plasma fibrinogen during LT in both groups, possibly explaining the lack of a significant between-group difference in outcomes. Although raising the target to 11 mm increased plasma levels of fibrinogen and MCF without affecting safety, this change provided no clinical benefits in this randomized multicenter trial.

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AUTHOR CONTRIBUTIONS

A.S., M.C., and A.B. designed the study. A.S., M.C., A.B., R.G., J.B., L.P., R.P., L.V., M.C., R.R., A.M., G.O., A.L., A.N., M.B., G.A., and G.P. performed the literature search and data collection. A.S., M.C., and A.B. performed the data analysis. A.S., M.C., A.B., R.G., J.B., L.P., R.P., L.V., M.C., R.R., A.M., G.O., A.L., A.N., M.B., G.A., and G.P. performed the data interpretation. A.S., M.C., and A.B. produced the figures. A.S. acquired the funding. A.S., M.C., and A.B. wrote the original draft; A.S. made subsequent revisions; and M.C. and A.B. reviewed the subsequent revisions. R.G., J.B., L.P., R.P., L.V., M.C., R.R., A.M., G.O., A.L., A.N., M.B., G.A., and G.P. approved the manuscript.

DECLARATION OF COMPETING INTEREST

A.S. received an honorarium from CSL Behring for a scientific lecture. A.B. received an honorarium from Octapharma for a scientific lecture. All other authors have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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