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Thromboelastography-Guided Blood Component Use in Patients With Cirrhosis With Nonvariceal Bleeding: A Randomized Controlled Trial

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Thromboelastography (TEG) provides a more comprehensive global coagulation assessment than routine tests (international normalized ratio [INR] and platelet [PLT] count), and its use may avoid unnecessary blood component transfusion in patients with advanced cirrhosis and significant coagulopathy who have nonvariceal upper gastrointestinal (GI) bleeding. A total of 96 patients with significant coagulopathy (defined in this study as INR >1.8 and/or PLT count < 50 × 10^9/L) and nonvariceal upper GI bleed (diagnosed after doing upper gastrointestinal endoscopy, which showed ongoing bleed from a nonvariceal source) were randomly allocated to TEG-guided transfusion strategy (TEG group; n = 49) or standard-of-care (SOC) group (n = 47). In the TEG group, only 26.5% patients were transfused with all three blood components (fresh frozen plasma [FFP], PLTs, and cryoprecipitate) versus 87.2% in the SOC group (P < 0.001). Although 7 (14.3%) patients in the TEG group received no blood component transfusion, there were no such patients in the SOC group (P = 0.012). Also, there was a significantly lower use of blood components (FFP, PLTs, and cryoprecipitate) in the TEG group compared with the SOC group. Failure to control bleed, failure to prevent rebleeds, and mortality between the two groups were similar. *Conclusion:* In patients with advanced cirrhosis with coagulopathy and nonvariceal upper GI bleeding, TEG-guided transfusion strategy leads to a significantly lower use of blood components compared with SOC (transfusion guided by INR and PLT count), without an increase in failure to control bleed, failure to prevent rebleed, and mortality. (Hepatology 2019;0:1-12).

Patients with cirrhosis have an imbalance of procoagulants and anticoagulants combined with potential alterations in fibrinolysis and platelet (PLT) number and function. These lead to altered values of standard laboratory coagulation test parameters. Standard assays of hemostasis (prothrombin time/international normalized ratio [PT/INR] and PLT counts) are frequently abnormal in cirrhosis, and these cannot evaluate the potential state of rebalanced status of the coagulation system because they only assess components of clot formation, and the other arm of coagulation (controlling the coagulation) remains undetected and therefore may provide misleading information regarding the risk of bleeding, possibly leading clinicians to administer unnecessary transfusions that could even be harmful in these sick patients.[(1)]

Abbreviations: CCT, conventional coagulation test; FFP, fresh frozen plasma; GI, gastrointestinal; ICU, intensive care unit; ILBS, Institute of Liver & Biliary Sciences; INR, international normalized ratio; MA, maximum amplitude; PLT, platelet; PT, prothrombin time; R time, reaction time; RBC, red blood cell; ROTEM, rotational thromboelastometry; SDAP, single-donor apheresis platelet; SOC, standard of care; TEG, thromboelastography; TRALI, transfusion-related acute lung injury; VHA, viscoelastic hemostatic assay.

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Traditionally, liver cirrhosis has been considered a prototype of hemorrhagic coagulopathy. However, studies have suggested that hemostasis in patients with liver disease exists in a state of rebalance in which defects in prohemostatic drivers are compensated for by commensurate changes in antihemostatic drivers.[2] This rebalanced status maintains a hemostatic balance despite abnormal values of laboratory-based coagulation tests in patients with compensated cirrhosis, and this balance can still continue or may be lost also in decompensated and advanced stages of liver cirrhosis, but it needs to be carefully evaluated before managing these patients. Viscoelastic hemostatic assays (VHAs), such as thromboelastography (TEG)/rotational thromboelastometry (ROTEM), have recently become available. TEG is a point-of-care, global hemostasis assessment device that measures the viscoelastic changes that occur during the hemostatic process, providing real-time reports. TEG is often normal in patients with compensated cirrhosis[3,4] and can display hypocoagulable features in patients with advanced cirrhosis.[5,6]

TEG is considered to be a more reliable test to assess coagulation than traditional tests (INR, PLTs) to guide transfusions in patients undergoing cardiac, trauma, and abdominal surgery and liver transplantation, and in patients with cirrhosis and significant coagulopathy undergoing invasive procedures.[7-15] A recently published systematic review and meta-analysis assessed the randomized controlled trials performed on patients in acute need of blood transfusions due to bleeding (not limited to liver disease patients), to evaluate the effect of VHA guidance on bleeding, transfusion requirements, and mortality. Fifteen randomized controlled trials with a total of 1,238 patients were included in this analysis. Of these trials, nine referred to cardiothoracic patients and one each to liver transplantation, surgical excision of burn wounds, trauma, cirrhosis, scoliosis surgery, and postpartum hemorrhage. In 12 studies, the intervention group was guided by TEG, and in the remaining three studies by ROTEM. The meta-analysis demonstrated no difference in survival between the groups with an odds ratio of 0.60 (95% confidence interval [CI], 0.34-1.07; $P = 0.08$). The amount of transfused fresh frozen plasma (FFP) was significantly reduced in the VHA-guided groups (a standardized mean difference of −1.98 [95% CI, −3.41 to −0.54]; $P = 0.007$), whereas no significant difference was found for PLT transfusion requirements.[15] In one study in patients with cirrhosis and significant coagulopathy before invasive procedures (60 patients were randomly allocated to TEG-guided transfusion strategy or standard of care [SOC] in a 1:1 ratio), all subjects in the SOC group received blood product transfusions versus 5 in the TEG group (100% versus 16.7%; $P < 0.0001$). TEG-guided transfusion strategy led to a significantly lower use of blood products compared with SOC (transfusion guided by INR and PLT count), without an increase in bleeding complications. The total amount of FFP infused was 4,000 mL (range, 0-2,000) in the TEG group and 17,750 mL (range, 0-1,200; median, 775) in the SOC group. None of the TEG group needed FFP alone, whereas 16 (53.3%) patients in the SOC group received FFP alone ($P < 0.0001$). The overall requirement of PLTs was 28 U (range, 0-6) in the TEG group and 106 U (range, 0-10; median, 0) in the SOC group. In the TEG group, 2 patients (6.7%) required PLTs versus 10 patients (33.3%) in the SOC group ($P = 0.021$).[12] In another study in the liver transplant setting, 28 patients undergoing orthotopic

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liver transplantation were randomized into two groups (i.e., those monitored during surgery using point-of-care TEG analysis [n = 14] and those monitored using standard laboratory measures of blood coagulation [n = 14]. In patients monitored by TEG, significantly less FFP was used (mean ± SD, 12.8 ± 7.0 units versus 21.5 ± 12.7 units). There was a trend toward less blood loss in the TEG-monitored patients; however, the difference was not significant. There were no differences in total fluid administration and 3-year survival.[14] In another nonrandomized study, which compared ROTEM with conventional coagulation tests (CCTs) to guide blood products during orthotopic liver transplantation, 34 patients who had transfusions guided by ROTEM were compared with 34 controls who received transfusions guided by CCTs. The ROTEM group had significantly less intraoperative blood loss (2.0 versus 3.0 L; $P = 0.04$) and FFP transfusion (4 versus 6.5 units; $P = 0.015$) compared with the CCT group (2.0 versus 3.0 L; $P = 0.04$). However, the total number of patients transfused with cryoprecipitate was increased in ROTEM (n = 25; 73%) compared with CCTs (n = 19; 56%; $P = 0.033$). The direct cost of blood products plus testing was reduced in the ROTEM group ($113,142.89 versus $127,814.77).[16]

Although variceal bleeding is the most common cause of upper gastrointestinal (GI) bleeding in patients with cirrhosis, nonvariceal sources are also important causes of upper GI bleed in these patients. Bleeding and impaired coagulation contribute significantly to the prognosis of patients with advanced liver cirrhosis, and there are no evidence-based blood component transfusion guidelines for coagulation correction among patients with advanced cirrhosis who bleed from nonvariceal sources.

The aim of the study was to assess the efficacy and safety of TEG in guiding the use of blood components in patients with advanced cirrhosis with nonvariceal bleeding and impaired traditional coagulation tests.

Patients and Methods

TRIAL DESIGN

This was a single-center, randomized, controlled trial.

PARTICIPANTS

The study was conducted in the Department of Hepatology and Liver Transplantation, Institute of Liver & Biliary Sciences (ILBS), New Delhi, from February 27, 2016, to March 3, 2018. The study was approved by the ILBS Institutional Review Board (#IEC2018/58/NA09). Informed consent was received from the participants, and the work was done in accordance with the Declaration of Helsinki.

Patients who fulfilled the following inclusion criteria were eligible to participate in the study: patients with advanced liver cirrhosis of any etiology; age between 18 and 80 years; presenting with nonvariceal upper GI bleeding (diagnosed after doing upper GI endoscopy, which showed ongoing bleed form a nonvariceal source); and significant coagulopathy assessed by CCTs (INR > 1.8 and/or PLTs < 50×10^9/L).

Exclusion criteria were the following: variceal bleed; postvariceal ligation ulcer bleed; previous or current thrombotic events defined as any documented blood clot in a venous or arterial vessel; anti-PLT or anticoagulant therapy at the time of enrollment or that had been discontinued less than 7 days before evaluation for the study; hemodialysis in the previous 7 days; pregnancy; and significant cardiopulmonary diseases.

INTERVENTIONS

After fulfilling all inclusion and exclusion criteria, patients were randomized to either the TEG or SOC group in a 1:1 proportion.

Patients in the TEG group received blood components using the following triggers: FFP at a dose of 10 mL/kg of ideal body weight when reaction time (R time) was greater than 10 minutes; a single-donor apheresis platelet (SDAP) unit, which corresponds to approximately 6 to 8 pooled units of PLTs, transfused when the maximum amplitude (MA) was less than 55 mm; and cryoprecipitate (5 pooled units) transfused when the alpha angle was less than 45°.[14]

In the SOC group, patients received FFP at the dose of 10 mL/kg of ideal body weight when the INR was greater than 1.8 and/or received PLTs in the amount of 1 SDAP when the PLT count was below 50×10^9/L.

Cryoprecipitate transfusions were given if fibrinogen concentrations were less than 80 mg/dL in the amount of 5 pooled units. INR, PLT count, and fibrinogen levels were assessed every 8 hours, and corrections were done accordingly (if patients continued to bleed).

To guarantee a better standardization and to avoid the interference of ascites and/or pleural effusion, the amount of FFP administered in both the TEG and SOC groups was calculated according to ideal body weight of the patient. Ideal body weight was calculated using the Devine formula as follows: male ideal body weight = 50 kg + 2.3 kg per inch over 5 feet; and female ideal body weight = 45.5 kg + 2.3 kg per inch over 5 feet.

FOLLOW-UP OF PATIENTS

At the time of randomization, demographic details and history and physical examination were done. Both groups of patients underwent the following investigations at baseline: hemogram; renal and liver function tests, including PT/INR; serum electrolytes; etiological workup for cirrhosis as needed; ultrasound abdomen with Doppler splenoportal axis and hepatic veins; blood sugar fasting; blood culture; urine culture; TEG; fibrinogen; and chest X-ray.

INR, PLT count, TEG, and fibrinogen were repeated every 8 hours. In the case of transfusion, the amount of blood components transfused, and transfusion-related side effects were recorded. Patients were assessed for control of bleeding and rebleeding until discharge from the hospital. After the discharge, patients were followed for up to 6 weeks.

OUTCOMES

The primary endpoint was the amount of FFP transfused in milliliters.

Secondary endpoints were as follows: (1) 5-day treatment failure (i.e., failure to control bleed); (2) failure to control rebleeding after 5 days; (3) amount of PLTs and cryoprecipitate transfused; (4) transfusion-related reactions; (5) duration of intensive care unit (ICU) and hospital stay; and (6) survival at 6 weeks.

SAMPLE SIZE

Reduction in FFP transfusion was used as the primary outcome to calculate sample size. We analyzed the data of consecutive 15 patients (patients with advanced cirrhosis with coagulopathy and nonvariceal upper GI bleed managed using conventional criteria for coagulation correction) before the start of this trial managed at ILBS, New Delhi, for the amount of FFP transfused. Up to 42 days after presentation, the mean ± SD of FFP was approximately 900 ± 400 mL. Assuming a 25% difference in the average transfusion requirement (900 ± 400 mL in the SOC group and 650 ± 300 mL in the TEG group) with a 5% alpha error and a 10% beta error, 43 patients in each group were required. Assuming a 10% dropout rate, it was planned to randomize 47 patients in each group.

RANDOMIZATION

Sequence Generation

Random allocation sequence was done by computer-generated random numbers code with an equal number of alternative treatments with a block size of 4. Patients were randomized to either of the two groups in a 1:1 ratio.

Allocation Concealment Mechanism

Sequentially numbered sealed, opaque, thick papered envelopes were used to conceal the sequence until interventions were assigned.

Implementation

The computer-generated random allocation sequence was generated by Mr. Kumar from the Information Technology Department; Dr. Bhardwaj from the Clinical Research Department assigned participants to interventions; Dr. Ahmad and Dr. Kumar from the Department of Hepatology and Liver Transplantation enrolled participants in the study; Dr. Bihari from the Department of Pathology did the interpretation of TEG; and statistical analysis was done by Dr. Kumar from the Department of Biostatistics.

Blinding

The participants, investigator clinicians, data collectors, and data analysts were blinded in this trial. The senior resident in charge of the ICU/ward decided on the blood product transfusion requirement according to the protocol.

STUDY ASSESSMENTS AND METHODS

TEG

A kaolin-activated TEG assay was performed with a 5000 series (Haemoscope, Inc., Niles, IL). The specific TEG variables used to guide blood component transfusions were R time, alpha angle, and MA. TEG was performed by industry-recommended parameters. For the TEG analysis, the sample required was 340 μL of sodium-citrated whole blood along with 20 μL of 0.2 mol/L of $CaCl_2$, and the test was required to be run after a wait of 30 to 40 minutes for maximum stability and within 1 hour of sample collection.

Ascites Grading

Grading of ascites was done as follows: grade 1 (mild ascites only detectable by ultrasound), grade 2 (moderate ascites evident by moderate symmetrical distension of abdomen), or grade 3 (large or gross ascites with marked abdominal distension).

Bleed-Related Events

Five-day treatment failure (i.e., failure to control bleed) and failure to prevent rebleeding after 5 days were defined according to Baveno VI and V criteria, respectively.[17,18]

Five-day treatment failure (i.e., failure to control bleed) was defined as death or need to change therapy, defined by one of the following criteria: fresh hematemesis or nasogastric aspiration of at least100 mL of fresh blood 2 hours or more after the start of a specific drug treatment or therapeutic endoscopy; development of hypovolemic shock; or 3 g drop in hemoglobin (9% drop of hematocrit) within any 24-hour period if no transfusion is administered.[17,18]

Failure to prevent rebleeding was defined as a single episode of clinically significant rebleeding after day 5, and clinically significant rebleeding was defined as recurrent melena or hematemesis resulting in any of the following: hospital admission, blood transfusion, 3 g drop in hemoglobin, or death within 6 weeks.[18]

Transfusion-Related Events

On the basis of reported signs and symptoms, transfusion medicine workup, and the reports of various investigations, the reactions were classified. All extended data forms and clinical synopses were reviewed independently by a panel of 3 experts (Dr. Maiwall, Dr. Bajpai, and Dr. Mitra) in a blinded fashion. Individual cases were assigned to 2 experts, and if, after independent review, they both agreed with the transfusion reaction diagnosis, the case was considered adjudicated and closed. If a diagnosis was not agreed upon, the third panel member independently reviewed the case. If the third reviewer agreed with 1 of the initial reviewers, the case was considered adjudicated and closed. If agreement on a diagnosis was not reached, a subsequent meeting was held among all expert panel members to reach agreement. To ensure the most accurate analysis, an imputability judged to be "definite" or "probable" by at least 1 expert panel member was required for classification of serious transfusion reactions. To categorize the cases, the expert panel relied on their clinical expertise plus criteria defined by the International Society of Blood Transfusion Working Party on Hemovigilance.[19]

For the purposes of this study, "serious" transfusion reactions included cardiopulmonary, hemolytic, septic, hypotensive, or anaphylactic reactions; and "minor" transfusion reactions included febrile nonhemolytic and minor allergic reactions. Minor transfusion reactions were not reviewed by the panel of experts.

Statistical Methods

Data were processed using the software package SPSS version 20.0. For comparison of categorical variables, chi-square and Fisher's exact tests were used. For comparison of continuous variables, Student *t* test was used for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. Kaplan-Meier curves for 42-day survival were plotted. All *P* values were two-sided, and a value of 0.05 was considered significant.

Results

PARTICIPANT FLOW

A total of 397 patients with advanced cirrhosis presenting with upper GI bleeding were screened for

eligibility, and after fulfilling the inclusion and exclusion criteria, 96 patients of nonvariceal bleed were randomized to either the TEG group (n = 49) or the SOC group (n = 47) (Fig. 1).

RECRUITMENT

The recruitment period for the trial was from February 27, 2016, to March 3, 2018. The trial was stopped after attainment of the appropriate sample size.

NUMBERS ANALYZED

A total of 49 patients in the TEG group and 47 patients in the SOC group were included in the analysis, and the analysis was performed using the original assigned groups.

OUTCOMES AND ESTIMATION

Baseline Data

Table 1 lists the baseline demographic, clinical, and biochemical characteristics of the enrolled patients. No significant differences in terms of age, sex, clinical features, cirrhosis prognostic scores, and clotting parameters were present between the two study groups at baseline. TEG parameters were similar in both groups.

Overall, 85 enrolled patients had an INR greater than 1.8 (43 of 49 [87.8%] in the TEG group and 42 of 47 [89.4] in the SOC group; P = 1.000); 79 had a PLT count less than 50 × 10^9/L (39 of 49 [79.6%] in the TEG group and 40 of 47 [85.1%] in the SOC group; P = 0.596); and 69 had INR greater than 1.8 and PLTs less than 50 × 10^9/L (34 of 49 [69.4%] in the TEG group and 35 of 47 [74.5] in the SOC group; P = 0.653).

Control of Bleeding, Duration of Hospital Stay, and Survival

At the end of 5 days of follow-up, failure to control bleeding was seen in 11 of 49 (22.4%) patients in the TEG group and 14 of 47 (29.8%) patients in the SOC group (P = 0.488). Of the 38 and 33 patients in the TEG and SOC groups, respectively, who showed control of bleed by day 5, failure to prevent rebleeding after day 5 occurred in 19 of 38 (50%) in the TEG group and 19 of 33 (57.6%) in the SOC group (P = 0.635) (Fig. 2 and Table 2).

Total ICU length of stay during the first admission was significantly shorter in the TEG group compared

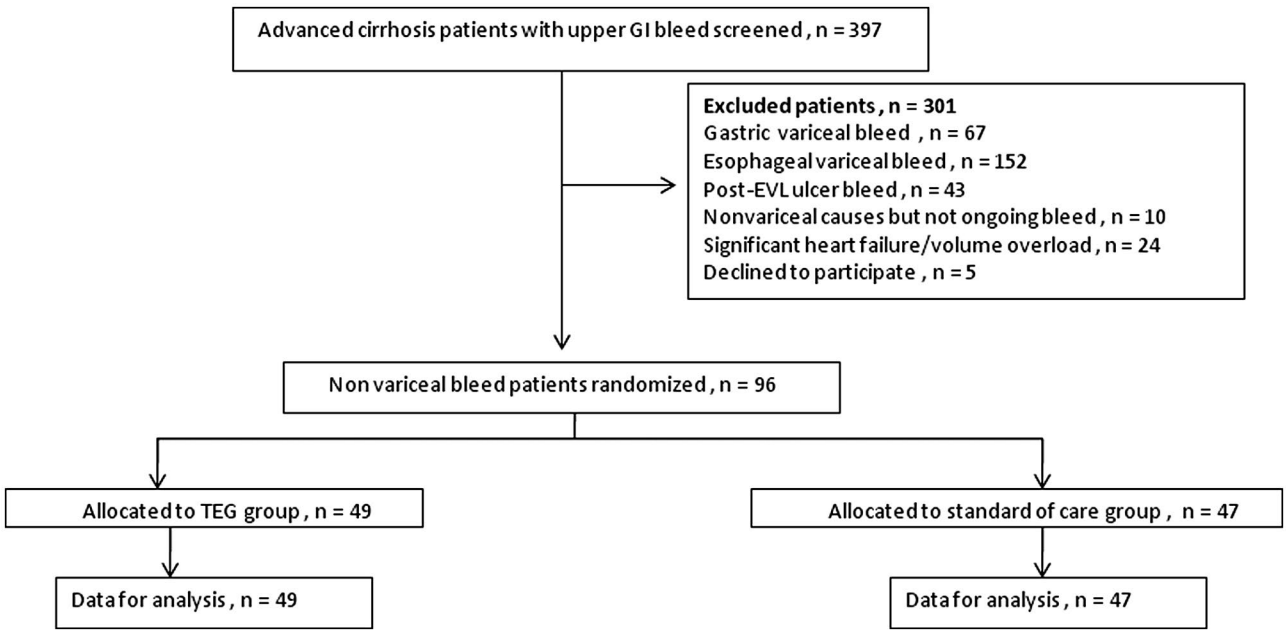

FIG. 1. Participant flow in the study. Abbreviation: EVL, endoscopic variceal ligation.

TABLE 1. Demographic, Clinical, and Biochemical Characteristics of Patients Enrolled

Characteristics	TEG Group (n = 49)	SOC Group (n = 47)	*P* Value
Age (years)	48 (29-72)	46 (29-67)	0.088
Male sex	36 (73.5)	42 (89.4)	0.066
Ideal body weight (kg)	67 (47-91)	68 (45-102)	0.860
Etiology			
Alcohol/NASH//HBV/HCV/other	24 (49)/8 (16.3)/7 (14.3)/6 (12.2)/4 (8.2)	24 (51.1)/11 (23.4)/5 (10.6)/5 (10.6)/2 (4.3)	0.822
Ascites			
None/Grade 1/Grade 2/Grade 3	8 (16.4)/11 (22.4)/17 (34.7)/13 (26.5)	5 (10.6)/12 (25.5)/18 (38.4)/12 (25.5)	0.858
Hepatic encephalopathy			
None/Grade 1/Grade 2/Grade 3/Grade 4	22 (44.9)/10 (20.4)/89 (16.3)/7 (14.3)/2 (4.1)	23 (48.9)/10 (21.3)/5 (10.6)/7 (14.9)/2 (4.3)	0.955
Prior bleeder	33 (70.2)	28 (57.1)	0.208
On NSBBs	39 (83.0)	34 (69.4)	0.158
Hemoglobin (gm/dL)	7.6 (4.3-12.5)	7.6 (4.4-12.3)	0.968
TLC, 10^9/L	11.7 (3.9-30.0)	11.2 (4.0-36.0)	0.222
Total bilirubin (mg/dL)	3.1 (0.8-36.0)	3.1 (0.8-39.9)	0.633
AST (IU/mL)	75 (25-609)	85 (32-299)	0.764
ALT (IU/mL)	43 (17-249)	35 (17-140)	0.618
ALP (IU/mL)	95 (18-211)	93 (16-290)	0.668
Albumin (gm/dL)	2.5 (1.3-3.7)	2.5 (1.4-3.7)	0.530
Blood urea (mg/dL)	56 (21-120)	57 (13-157)	0.450
Serum creatinine (mg/dL)	0.99 (0.3-3.01)	0.91 (0.25-2.5)	0.256
Sodium (mEq/L)	129 (118-139)	130 (118-155)	0.588
INR	2.6 (1.15-4.12)	2.5 (1.6-4.62)	0.849
INR > 1.8	43 (87.8)	42 (89.4)	1.000
Platelets, 10^9/L	40 (16-133)	37 (19-119)	0.298
Platelets < 50×10^9/L	39 (79.6)	40 (85.1)	0.596
INR > 1.8 and platelets < 50×10^9/L	34 (69.4)	35 (74.5)	0.653
Fibrinogen (mg/dL)	45 (21-89)	43 (22-112)	0.452
Fibrinogen < 80 mg/dL	48 (98)	42 (89.4)	0.108
MAP (mm Hg)	60 (50-108)	58 (50-65)	0.927
HR (per minute)	111 (88-126)	110 (93-126)	0.324
MELD score	23 (11-40)	21 (11-38)	0.572
Lactate	4.8 (3.2-27.0)	4.8 (2.4-8.5)	0.431
TEG parameters			
R (min)	14 (6-19)	13 (7-19)	0.871
R > 10 min	30 (61.2)	29 (61.7)	1.000
K (min)	10 (3-14)	10 (3-13)	0.956
α-angle (°)	44 (20-89)	44 (23-89)	0.965
α-angle < 45°	30 (61.2)	29 (61.7)	1.000
MA (mm)	53 (23-76)	53 (23-77)	0.754
MA < 55 mm	26 (53.1)	25 (53.2)	1.000
LY30 (%)	3 (1-15)	4 (1-14)	0.576
Cause of bleeding			0.867
Erosive gastritis	8 (16.3)	9 (19.1)	
PHG	17 (34.7)	18 (38.3)	
PHG + GAVE	4 (8.2)	4 (8.5)	
Isolated GAVE	5 (10.2)	3 (6.4)	
Gastric ulcer	4 (8.2)	5 (10.6)	
Duodenal ulcer	10 (20.4)	7 (14.9)	

TABLE 1. *Continued*

Characteristics	TEG Group (n = 49)	SOC Group (n = 47)	*P* Value
Mallory-Weiss tear	1 (2.0)	0 (0)	
Severe esophagitis	0 (0)	1 (2.1)	

Note: Data are n (%) or median (range).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GAVE, gastric antral vascular ectasia; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, heart rate; K, amplification time; LY30, clot lysis in 30 minutes; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; min, minutes; NASH, nonalcoholic steatohepatitis; NSBB, nonselective beta-blocker; PHG, portal hypertensive gastropathy; R, initiation time; TLC, total leukocyte count.

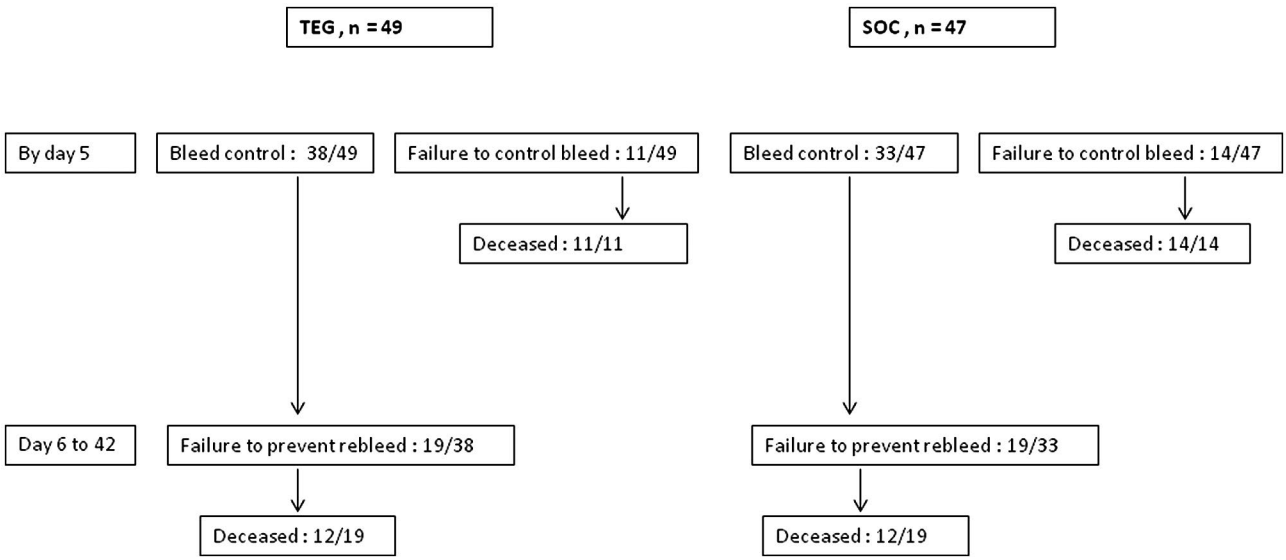

FIG. 2. Failure to control bleeding by day 5 and failure to prevent rebleeding after day 5 in the TEG and SOC groups during 42 days of follow-up. There was no significant difference in 5-day and 42-day mortality between the two groups.

with the SOC group (median [range] 2 [1-10] days and 3 [1-8] days, respectively; $P = 0.012$). Total hospital length of stay during the first admission was similar between the two groups (Table 2).

The number of patients who were discharged from the hospital after the first admission was 34 of 49 (69.4%) in the TEG group and 23 of 47 (48.9%) in the SOC group. Of these, 19 of 34 (55.9%) in the TEG group and 13 of 23 (56.5%) in the SOC group were readmitted. However, there was no significant difference in the total ICU and total hospital length of stay (up to 42 days) between the two groups (Table 2).

There was no significant difference in 5-day and 42-day mortality between the two groups (Table 2 and Fig. 2). Kaplan-Meier curve analysis also showed no survival differences between the groups ($P = 0.180$; Fig. 3).

BLOOD COMPONENTS TRANSFUSED

The total amount of FFP infused per patient was 440 mL (0-1,320 mL) in the TEG group and 880 mL (0-1,640 mL) in the SOC group ($P < 0.001$) (Table 3). Overall requirement of PLTs per patient was 1 (0-1) SDAP unit in the TEG group and 2 (0-3) units in the SOC group ($P < 0.001$). Similarly, the total amount of cryoprecipitate infused per patient was significantly less in the TEG group (4 [0-24] units) compared with the SOC group (16 [4-36] units); $P < 0.001$ (Table 3).

TABLE 2. Control of Bleeding, Length of Hospital Stay, and Survival in TEG and SOC Groups During 42 Days of Follow-Up

Variable	TEG Group (n = 49)	SOC Group (n = 47)	*P* Value
Failure to control bleeding by day 5	11 (22.4)	14 (29.8)	0.488
Failure to prevent rebleeding after day 5 (among patients whose bleed was controlled by day 5)	19 of 38 (50)	19 of 33 (57.6)	0.635
Total ICU length of stay in first admission (days)	2 (1-10)	3 (1-8)	0.012
Total hospital length of stay in first admission (days)	5 (1-13)	5 (1-21)	0.750
Discharged from hospital after first admission	34 (69.4)	23 (48.9)	0.061
Readmission after first discharge (among patients who got discharged after first admission)	19/34 (55.9)	13/23 (56.5)	1.0
Total ICU length of stay up to 42 days (days)	4 (1-12)	4 (1-20)	0.638
Total hospital length of stay up to 42 days (days)	7 (1-21)	6 (1-21)	0.822
5-day mortality	11 (22.4)	14 (29.8)	0.488
42-day mortality	27 (55.1)	31 (66)	0.303

Note: Data are n (%) or median (range).

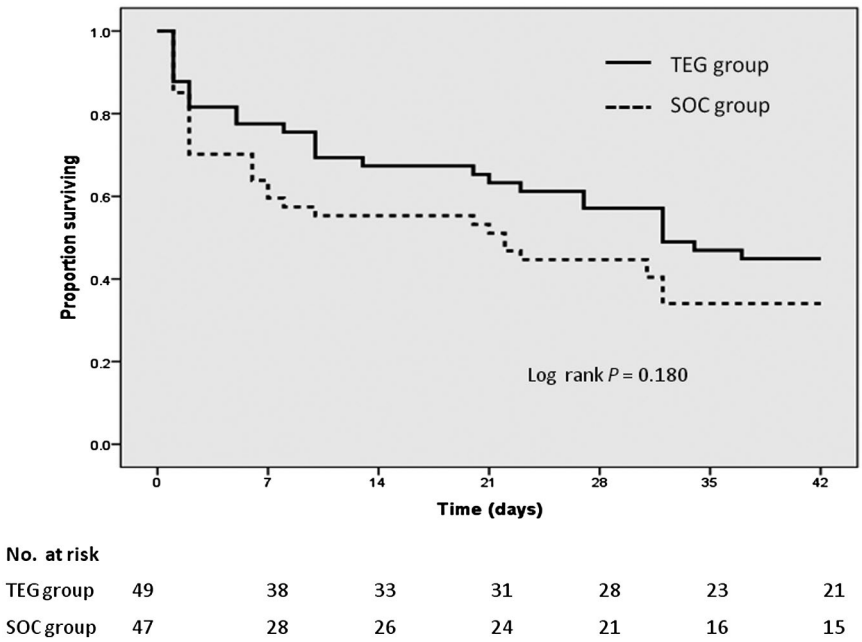

FIG. 3. Kaplan-Meier analysis of survival between the TEG and SOC groups. There was no significant survival difference between the two groups ($P = 0.180$).

In the TEG group, 13 of 49 (26.5%) patients were transfused with all three blood components (FFP, PLTs, and cryoprecipitate) versus 41 of 47 (87.2%) in the SOC group ($P < 0.001$). Seven patients (14.3%) in the TEG group and none in the SOC group received no blood components (FFP, PLTs, or cryoprecipitate) ($P = 0.012$).

However, there was no significant difference between the two groups with respect to the number of patients transfused with red blood cells (RBCs), total amount (packs) of RBCs transfused, or RBCs transfused (packs) per patient (Table 3).

TRANSFUSION-RELATED SIDE EFFECTS

Overall, serious transfusion-related reactions were significantly less in the TEG group, with 15 (30.6%)

TABLE 3. Distribution of Blood Products Transfused and Transfusion-Related Side Effects in TEG and SOC Groups During 42 Days of Follow-Up

Variable	TEG Group (n = 49)	SOC Group (n = 47)	*P* Value
Total amount of FFP infused (mL)	20,860	40,300	< 0.001
FFP (mL) infused/patient	440 (0-1,320)	880 (0-1,640)	< 0.001
Total amount of platelet pools infused (U)	26	71	< 0.001
Platelet pools (U) infused/patient	1 (0-1)	2 (0-3)	< 0.001
Total amount of cryoprecipitate infused (U)	278	814	< 0.001
Cryoprecipitate (U) infused/patient	4 (0-24)	16 (4-36)	< 0.001
Transfused FFP only	2 (4.1)	0 (0)	0.495
Transfused platelets only	2 (4.1)	0 (0)	0.495
Transfused cryoprecipitate only	6 (12.2)	0 (0)	0.027
Transfused FFP and platelets	7 (14.3)	0 (0)	0.012
Transfused FFP and cryoprecipitate	8 (16.3)	4 (8.5)	0.357
Transfused platelets and cryoprecipitate	4 (8.2)	2 (4.3)	0.678
Transfused FFP, platelets, and cryoprecipitate	13 (26.5)	41 (87.2)	< 0.001
No FFP, platelets, or cryoprecipitate	7 (14.3)	0 (0)	0.012
Transfused RBCs	40 (81.6)	35 (74.5)	0.464
Total amount of RBCs transfused (packs)	118	126	0.584
RBCs transfused (packs) per patient	2 (0-7)	2 (0-10)	0.584
Any serious transfusion-related reaction	15 (30.6)	35 (74.5)	< 0.001
TRALI	6 (12.2)	23 (48.9)	< 0.001
TACO	5 (10.2)	10 (21.3)	0.166
ARDS	1 (2)	9 (17)	0.011
Other serious transfusion reactions	3 (6.1)	13 (27.7)	0.006

Note: Data are n (%) or median (range).
Abbreviations: ARDS, acute respiratory distress syndrome; TACO, transfusion-associated circulatory overload.

patients developing any transfusion-related reaction compared with 35 patients (74.5%) in the SOC group ($P < 0.001$).

Incidence of transfusion-related acute lung injury (TRALI) and acute respiratory distress syndrome was significantly less in the TEG group compared with the SOC group (Table 3). TRALI developed in 6 (12.2%) patients in the TEG group compared with 23 (48.9%) patients in the SOC group ($P < 0.001$).

Discussion

Cirrhosis is characterized by decreased synthesis of both procoagulants and anticoagulants, whose delicate balance is further weakened by thrombocytopenia and/or thrombocytopathy.[20] These abnormalities result in prolongation of PT and of activated partial thromboplastin time, all of which have led in the past to cirrhosis being considered a prototypical hemorrhagic disorder.[21] Views on the clotting status of patients with cirrhosis have had a major recent change: They are now considered at a higher risk of thrombotic, rather than hemorrhagic, complications.[22]

There are no clear guidelines regarding coagulopathy and thrombocytopenia correction during bleeding episodes from nonvariceal sources in patients with advanced cirrhosis.[17,23] The aim of our study was to determine whether a TEG-guided transfusion strategy, using a more accurate method to reflect coagulopathy, would lead to a significantly lower use of blood components compared with standard practice (transfusion guided by INR and PLT count) in acute nonvariceal bleed among patients with advanced cirrhosis.

We found that the blood component volume (in the form of FFP, PLTs, and cryoprecipitate) was significantly lower when using TEG to guide transfusion of blood components. Also, in the TEG group, only 26.5% patients were transfused with all three blood components (FFP, PLTs, and cryoprecipitate) versus 87.2% in the SOC group ($P < 0.001$). Although there were no patients in the SOC group who received no

blood components (FFP, PLTs, or cryoprecipitate), there were 7 (14.3%) such patients in the TEG group (P = 0.012). TEG is considered to be a more reliable test to assess coagulation than CCTs (INR and PLTs) to guide transfusion in patients undergoing liver transplantation.[8,10,14] One study found that TEG-guided transfusion decreases transfusion of FFP in patients undergoing orthotopic liver transplantation, but does not affect 3-year survival.[11] In addition, TEG-guided transfusion strategy has been found to be associated with a significantly lower use of blood components compared with transfusion guided by INR and PLT count, without an increase in bleeding complications, in patients with cirrhosis and significant coagulopathy undergoing invasive procedures.[12,13]

Overall, serious transfusion-related reactions were significantly less in the TEG group, with 15 (30.6%) patients developing any transfusion-related reaction compared with 35 patients (74.5%) in the SOC group (P < 0.001). TRALI developed in 29 (30.2%) patients (6 [12.2%] patients in the TEG group compared with 23 [48.9%] in the SOC group [P < 0.001]). In one recent study assessing TRALI in ICU patients admitted with GI bleeding, it was found that transfused patients with end-stage liver disease (n = 72) developed TRALI more frequently than those without end-stage liver disease (29% versus 1%; P < 0.01).[24]

No difference in failure to control bleed and survival was found between the TEG and SOC groups, and this further underlies that TEG-directed decision making in replacement needs of blood components is as safe as the traditional criteria.

There are no studies comparing the influence of different laboratory trigger points (both by using TEG parameters and standard coagulation tests) on the amount of blood component transfused in the context of nonvariceal bleeding. Significantly more units of FFP were transfused using an INR of greater than 1.8 compared with the TEG R time of greater than 10 minutes. Similarly, more PLTs were transfused using PLTs less than 50 × 10^9/L compared with TEG MA less than 55 mm, and more cryoprecipitate was transfused using a fibrinogen of less than 80 mg/dL compared with TEG alpha angle less than 45°. However, it is possible that these thresholds are too conservative for patients with advanced cirrhosis with upper GI bleeding. This study was not designed to examine how well a linear array of laboratory values predicted the amount of blood component administered. Additional studies are needed to identify the predictive values for a range of trigger points based on TEG parameters and CCTs. It remains to be seen whether the threshold TEG parameters (trigger points) we chose for transfusion of blood components could be further relaxed to pick up patients with more severe coagulopathy, and thus further reduction in the need for blood component transfusion.

There are some limitations of this study. Levels of individual clotting factors and PLT function tests before and after blood component transfusion were not done.

In conclusion, among patients with advanced cirrhosis with coagulopathy and nonvariceal upper GI bleeding, TEG-guided transfusion strategy leads to a significantly lower use of blood components compared with SOC (transfusion guided by INR and PLT count), without an increase in failure to control bleed, failure to prevent rebleed, and mortality.

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