Usefulness of thromboelastometry in predicting the risk of bleeding in cirrhotics who undergo invasive procedures

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Objectives The management of patients with liver cirrhosis undergoing invasive procedures is controversial and haemostasis assessment using routine laboratory is inappropriate. We evaluated the following: (a) the ability of thromboelastometry to predict the risk of bleeding in cirrhotic patients undergoing invasive procedures and enable a decision on the prophylactic transfusional strategy; (b) the contribution of platelet adhesion and aggregation tests in the assessment of haemostasis.
Patients and methods Seventeen cirrhotic patients undergoing invasive procedures were analyzed retrospectively (training set). To obtain preliminary data, an observational study was carried out in 58 patients (test set). All 75 patients were evaluated by thromboelastometry. Platelet adhesion and aggregation were evaluated in 16 patients using Multiplate, PFA-100 and Light Transmission Aggregometry. Factor VIII was dosed in all patients of the test set.
Results In the training set, thromboelastometry confirmed the haemostatic assessment shown by the conventional test only in 6/17 (35%) patients. In the test set, thromboelastometry identified all patients who had a bleeding event. In patients with a high risk of bleeding, the use of thromboelastometry was cost-effective, reducing the platelet infusions by 64%. Platelet adhesion/aggregation abnormalities were observed in 15/16 (94%) patients, but bleeding events occurred only in 2/15 (13%) patients.
Conclusion Thromboelastometry appears to be useful to screen cirrhotic patients undergoing invasive procedures to identify the risk of bleeding and to optimize the transfusional strategy. Adhesion/aggregation tests are not useful in identifying patients at risk of bleeding and their application is not cost-effective. Eur J Gastroenterol Hepatol 27:1313–1319

Introduction

End-stage liver disease is characterized by a complex haemostatic profile involving different phases of haemostasis such as thrombocytopenia, platelet function defects, decreased synthesis of procoagulant factors and hyperfibrinolysis [1–5]. These alterations have always been considered responsible for haemorrhagic diathesis in cirrhotic patients. In reality, these patients show not only a low incidence of bleeding events but also an increased risk of thrombosis [6–8]. This phenomenon can be explained by a 'rebalance' of the coagulation system, characterized by an increase in circulating levels of von Willebrand factor and factor VIII associated with a reduced synthesis of anticoagulant factors [9–11]. Nevertheless, in cirrhotic patients, this 'rebalanced' system is unstable and can easily be perturbed by acute events such as infections, variceal bleeding and renal dysfunction [12]. Because of these complex changes and the heterogeneity among different patients, it is usually difficult for clinicians to identify patients with a true risk of bleeding. In this context, conventional coagulation tests such as international normalized ratio (INR) and platelet count are inadequate, mainly because they examine only single elements of haemostasis. Thromboelastometry (TEM) enables a global evaluation of haemostasis from clot formation to its lysis, measuring the interaction of plasmatic factors and cellular components. In stable cirrhosis, TEM parameters are related to markers of liver impairment [13,14]. Recent clinical trials have shown the usefulness of TEM in different clinical settings. In the hepatologic field, TEM is used routinely to enable a decision on the transfusion strategy during liver transplant [15]. Platelet adhesion and aggregation defects are often observed in patients with cirrhosis and they can contribute towards haemostatic abnormalities. Despite this, the real utility of platelet function assays in clinical practice is still not clear [5].

In our study, we evaluated the ability of TEM to identify the risk of bleeding in cirrhotic patients undergoing invasive procedures and its potential role in guiding the prophylactic transfusion strategy in comparison with conventional coagulation tests and the usefulness of second-level analysis (Multiplate, Platelet Function Analyzer-100/PFA-100 and Light Transmission Aggregometry) to analyse platelet function in these patients. This was an observational study based on daily clinical practice. Patients were assessed by standard

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tests used normally and the decision to transfuse blood products was made on the basis of standard test results, clinical condition and the type of procedure. At the same time, TEM was performed in all patients to assess whether and how our clinical approach could be changed.

Patients and methods

The study was approved by the Local Institutional Ethics Committee.

Patients

A total of 75 adult cirrhotic patients undergoing invasive procedures and presenting to the Gastroenterology and Hepatology Unit, San Giovanni Battista Hospital (Turin, Italy) were enrolled in the study after they signed an informed consent. The diagnosis of cirrhosis was made on the basis of clinical, biochemical, radiological or histological evidence. Evidence of active disseminated intravascular coagulation and a clinical history positive for hereditary coagulopathies or thrombophilia were the exclusion criteria.

Seventeen out of 75 patients were analysed retrospectively (training set) (Table 1). According to data obtained in the training set (TEM abnormalities also in patients with mild alterations in conventional tests), 58 patients were enrolled and analysed prospectively (test set).

Patients in the test set were divided according to the severity of coagulative disorder established using conventional coagulation tests: 32 patients in group A, 20 patients in group B and six patients in group C. This stratification was performed to evaluate whether TEM was useful to identify patients at high risk of bleeding despite mild alterations in INR or platelet count. Group A included patients requiring a prophylactic infusion of blood products according to local guidelines (platelet count < 50 000/mm^3 and/or INR > 1.8). Group B included patients in whom haemostatic abnormalities were frequently detected by TEM analysis in the training set (platelet count between 50 000 and 100 000/mm^3 and INR between 1.5 and 1.8). Patients with minimal abnormalities in platelet count and INR were included in group C (Table 2).

Table 1. Clinical and biochemical characteristics of patients included in the training set

Patients (*n*)	17
Sex (male/female)	11/6
Age (years)	62 (26–81)
Aetiology (*n*)	
Viral	12
Alcoholic	1
Autoimmune	1
Others	3
Child A/B/C	10/3/4
INR	1.4 ± 0.5
Platelets (/mm^3)	92 470 ± 45 540
Creatinine (mg/dl)	0.82 ± 0.6
Decompensated cirrhosis	6/17
Type of procedure	
CVC	3
TACE	6
VL	3
RFA	5

Values are expressed as median (range) or mean (SD).
CVC, central venous catheter; INR, international normalized ratio; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; VL, variceal ligation.

Methods

Global haemostasis was evaluated by TEM. Rotational TEM was carried out using a ROTEM Delta (Tem Innovations GmbH, Munich, Germany) device according to the manufacturer's instructions. We analysed the following: clotting time (CT) (in s), time from the beginning of the test to a trace's amplitude of 2 mm; clot formation time (CFT) (in s), time from an amplitude of 2 mm to an amplitude of 20 mm; and maximum clot firmness (MCF) (in mm), the maximal amplitude reached before the lysis of the clot begins.

CT, CFT and MCF were measured as EXTEM, INTEM or FIBTEM. EXTEM reflects the functionality of the extrinsic and common pathways of coagulation, whereas INTEM reflects that of intrinsic and common pathways. FIBTEM describes the role of fibrinogen in clot formation. A prolonged INTEM/EXTEM CT indicates a deficiency of coagulation factors. A CFT prolonged or MCF reduced in INTEM/EXTEM is associated with a reduced MCF FIBTEM, and a fibrinogen deficiency or fibrin polymerization disorders are the most likely potential causes of bleeding; however, if, under the same condition, FIBTEM MCF is normal, a low platelet count or severe platelet dysfunction should be suspected.

In EXTEM, haemostasis is triggered by tissue factor, in INTEM by ellagic acid and in FIBTEM by ellagic acid and cytochalasin D (inhibiting platelet function). Normal values of such parameters (provided by the manufacturer and used by the Essener–Runde task force) are described in Table 3 [16].

Platelet aggregation and adhesion were evaluated as follows:

(1) Whole-blood impedence aggregometry (Multiplate; Roche Diagnostics International Ltd, Risch-Rotkreutz, Switzerland) according to the manufacturer's instructions. We performed the following tests: the ASPI test (platelet aggregation is triggered by arachidonic acid) and the RISTO low test (platelet aggregation is triggered by ristocetin).
(2) Light Transmission Aggregometry (PAP-8E; Bio/Data Corporation, Horsham, Pennsylvania, USA) according to the manufacturers' instructions. ADP (2.5–5–10 μmol/l), collagen (2.5–5 μg/ml), arachidonic acid (250–500 μg/ml) and ristocetin (1000–1200–1500 μg/ml) were used as reactants.
(3) PFA-100 (Siemens Healthcare Diagnostic, Tarrytown, New York, USA). Collagen and epinephrine as well as collagen and ADP were used to trigger adhesion according to the manufacturer's instructions.

Whole-blood coagulation was assessed in all 75 patients using TEM before performing the invasive procedure. In the test set, post-transfusional thromboelastometric analysis was carried out in nine patients. The guidelines of our centre make provisions for a prophylactic infusion of platelets with a platelet count less than 50 000/mm^3 and the use of fresh frozen plasma when INR is more than 1.8 or fibrinogen is less than 100 mg/dl [17,18]. Platelet aggregation and adhesion were evaluated in 16 patients in the test set (12 in group A and four patients in groups B

Table 2. Clinical and biochemical characteristics of patients included in the test set

	Group A[a] PLTs $<50\,000/mm^3$ + INR > 1.8 PLTs $<50\,000/mm^3$ + INR < 1.8 PLTs $>50\,000/mm^3$ + INR > 1.8	Group B PLTs 50 000–100 000/mm^3 + INR 1.5–1.8	Group C PLTs > 100 000 mm^3 + INR < 1.5
Patients (*n*)	32	20	6
Sex (male/female)	21/11	14/6	4/2
Age (years)	51 (37–82)	67.5 (44–80)	62.5 (55–70)
Aetiology			
Viral	17	12	1
Alcoholic	3	2	3
Viral + alcoholic	2	0	0
Autoimmune	6	1	1
Others	4	3	2
Child A/B/C	4/11/17	7/10/3	4/2/0
Meld	20.6 ± 8.7	14 ± 4.8	9.5 ± 2.7
Decompensated cirrhosis	22 (68.8)	9 (45)	1 (16.7)
Hepatocarcinoma	8 (15.7)	3 (15.0)	1 (16.7)
Portal vein thrombosis	8 (25)	4 (20)	1 (16.7)
Bilirubin (mg/dl)	7.6 ± 11.4	2.5 ± 2.7	1.4 ± 1.1
Albumin (g/dl)	2.9 ± 0.5	3.2 ± 0.6	3.7 ± 0.9
Creatinine (mg/dl)	1.1 ± 0.6	1.2 ± 0.7	0.8 ± 0.1
Ht (%)	29.4 ± 5.8	34.3 ± 5.3	39.1 ± 6.1
WBC ($\times 10^9$/l)	5.4 ± 4.0	5.1 ± 2.4)	7.2 ± 2.2
PLTs (/mm^3)	53 518 ± 34 899	73 110 ± 14 493	143 660 ± 46 603
INR	1.99 ± 0.69	1.36 ± 0.16	1.16 ± 0.13
Fibrinogen (mg/dl)	192.9 ± 74.8	216 ± 51.8	342.2 ± 63.9
Factor VIII (%)	141.4 ± 42.8	138.1 ± 38.1	163.0 ± 39.0
Type of procedure			
VL	7	6	3
Paracentesis	5	5	0
TIPS	4	2	0
TACE	2	1	1
CVC	3	0	0
RFA/MW for HCC	3	3	1
Dental extraction	2	1	0
Duodenal polypectomy	1	1	0
Abdominal catheter	1	0	0
Cholecystectomy	1	1	0
Cardiac catheterisation	3	0	0
Larynx biopsy	0	0	1

Values are expressed as mean ± SD or median (range).
CVC, central venous catheter; Ht, haematocrit; HCC, hepatocarcinoma; INR, international normalized ratio; MW, microwaves; PLTs, platelets; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TIPS, transjugular intrahepatic portosystemic shunt; VL, variceal ligation; WBC, white blood cell.
[a]Group A: patient fulfilling the criteria required for prophylactic transfusion according to local guidelines.

Table 3. Normal values of thromboelastometry parameters

Tests	CT	CFT	MCF
EXTEM	38–79 s	34–159 s	50–72 mm
INTEM	110–240 s	30–110 s	50–72 mm
FIBTEM	–	–	9–25 mm

CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness.

and C). Circulating levels of factor VIII were measured in all patients.

Statistical analyses

For binary categorical data, Fisher's test of exact probability was used. Student's *t*-test was used to compare TEM parameters between groups A, B and C and to compare factor VIII levels in patients with and without portal vein thrombosis. The Wilcoxon signed-rank test was used to evaluate the difference in TEM parameters before and after a prophylactic infusion of blood products. *P* values less than 0.05 were considered statistically significant. All analyses were carried out using SPSS (10; SPSS Inc., Chicago, Illinois, USA) statistical package for Windows.

Results

Training set

Data from these 17 patients were analysed retrospectively and represent the preliminary results of the study. They suggest that INR and platelet count are not related to intraoperative or postoperative bleeding (two haemorrhagic events occurred, one in a patient with an INR value of 1.6 and the other with an INR value of 2.5). Moreover, TEM parameters showed normal clot formation in 1/4 (25%) of patients with platelets less than 50 000/mm^3 and/or INR more than 1.8 and abnormalities in clot formation in 8/13 (61.5%) patients with mild alteration of conventional tests, indicating abnormalities in particular in patients with platelet count between 50 000 and 100 000/mm^3 and INR between 1.5 and 1.8. TEM confirmed the haemostatic assessment detected by standard coagulation tests in only 6/17 (35%) patients. Transfusions were performed in three patients, all with a normal TEM analysis. As mentioned previously, two patients developed bleeding: both of them had abnormal clot formation according to TEM, but only one of them had an INR value more than 1.8. Using TEM in the preprocedural transfusion strategy could have modified the approach in 65% of cases.

According to these observations, we continued our study by analysing prospectively another group of 58 patients.

Test set

Thromboelastometry and risk of bleeding

Postprocedural haemorrhagic events (defined as any bleeding event referred to the consultants, and in particular: haematoma, haematemesis/melena, abdominal pain associated with a significant reduction in haemoglobin levels, at least 1 g/dl) occurred in 6/58 (10.3%) patients. Four patients in group A (12.5%) developed bleeding after duodenal biopsy, dental extraction, abdominal catheter positioning and variceal ligation, respectively, and in two (10%) patients in group B after cholecystectomy and transarterial chemoembolization. No episodes were observed for group C. Unlike standard coagulation parameters, the profile of TEM was abnormal in all patients with a bleeding event.

Interestingly, bleeding episodes were also reported in group B. Patients of this group would not receive prophylactic infusional therapy according to the current guidelines. We decided to analyse which TEM parameters could help discriminate groups A and B (in which haemorrhage episodes occurred) from group C. Statistically significant abnormalities in MCF were found in groups A and B compared with group C in all tests (EXTEM, INTEM and FIBTEM). CFT was significantly prolonged in groups A and B compared with group C only in the EXTEM test (Table 4).

Thromboelastometry and prophylactic transfusion strategy

In patients of group A, prophylactic platelets infusion was needed in 25/32 (78%) patients according to standard coagulation parameters, whereas only nine (28%) patients required the same treatment according to TEM parameters. The difference was statistically significant ($P = 0.0001$). Considering prophylactic infusion of plasma, 18/32 (56%) patients required an infusion according to standard coagulation tests. In only 12 (66%) of them, TEM confirmed the necessity of plasma infusion, whereas in seven patients, only a reduction in MCF FIBTEM was found showing a prevalent fibrinogen disorder. If TEM parameters had been used to make the decision of prophylactic transfusion in our patients, there would have been a 64% reduction in the use of platelet pools and an optimal use of plasmatic coagulation factors.

Of note, an impairment in fibrin polymerization was suspected in 5/6 (83%) patients who had bleeding compared with 18/52 (34%) of patients who did not have bleeding ($P < 0.05$). Patients who had bleeding had a very low MCF FIBTEM (< 8 mm, mean 5.8 mm), despite a normal plasmatic level of fibrinogen (154 mg/ml, range 112–223 mg/ml). Patients without bleeding had higher plasmatic fibrinogen levels than patients with bleeding (219.5 mg/ml, range 70–429 mg/ml; $P < 0.01$). In group A, three patients had platelet count 100 000/mm^3 or more and INR 1.8 or more (3.03, 2.07 and 1.88, respectively). In all of these patients, the prophylactic infusion of plasma would be recommended according to a conventional coagulation test. Conversely, TEM analysis indicates normal clot formation in these patients, not showing a clear indication for prophylactic transfusion.

According to conventional coagulation tests, none of the patients in groups B and C had a significant risk of bleeding and needed prophylactic transfusion. In contrast, in group B, TEM analysis showed abnormalities in clot formation in 8/20 (40%) patients. Two of these patients developed bleeding.

In nine patients, we measured TEM parameters before and after the prophylactic infusion of blood products. We observed a statistically significant improvement in TEM parameters CFT and MCF EXTEM, CT and MCF INTEM, but none of the patients showed normalization of haemostasis assessed by TEM after the infusion of blood products (Table 5).

Results suggest that an individual approach could be rational in the treatment of coagulation disorders detected by TEM in cirrhotic patients candidate to invasive procedures (Table 6).

Thromboelastometry and portal vein thrombosis

Thirteen of the enrolled patients had non-neoplastic portal vein thrombosis, identified using imaging techniques (abdominal ultrasonography, computed tomography scan). Eight of them belonged to group A, four to group B and one to group C. In none of them did TEM show a pattern of hypercoagulability. Furthermore, on comparing factor VIII values of patients with and without portal vein thrombosis, we observed that the mean value was higher in

Table 4. Comparison of thromboelastometry parameters between different groups

	Group A ($N = 32$)	Group B ($N = 20$)	Group C ($N = 6$)
EXTEM			
CT	67.4 ± 20.5	51.8 ± 7.0	52.2 ± 3.6
CFT	333.3 ± 250.1†	159.0 ± 43.0‡	92.5 ± 33.0
MCF	40.0 ± 10.7†	49.3 ± 4.8‡	56.8 ± 6.2
INTEM			
CT	215.4 ± 48.9	188.7 ± 32.0	184.5 ± 38.8
CFT	276.5 ± 167.6†	136.5 ± 48.6	104.0 ± 43.8
MCF	39.4 ± 11.9†	47.6 ± 9.1‡	57.7 ± 6.0
FIBTEM			
MCF	8.4 ± 4.9†	10.9 ± 3.5‡	15.8 ± 5.0

Values are expressed as mean ± SD.
CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness.
†$P < 0.05$ group A compared with group C.
‡$P < 0.05$ group B compared with group C.

Table 5. Thromboelastometry parameters measured before and after the prophylactic infusion of blood products

	Before infusion	After infusion	*W* value
EXTEM			
CT	76.9 ± 24.4	65.9 ± 15.6	8
CFT	497.2 ± 346.5	279.9 ± 135.8	0
MCF	32.9 ± 8.1	39.4 ± 6.5	0
INTEM			
CT	197.4 ± 21.9	182.4 ± 18.8	2
CFT	273.3 ± 98.3	213 ± 82.6	6
MCF	36.2 ± 5.0	40 ± 4.7	0
FIBTEM			
MCF	7.9 ± 4.3	6.2 ± 4.3	13.5

Values are expressed as mean ± SD.
The *W* value was considered statistically significant when < 5.
CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness.

Table 6. Individual therapeutic approach to treat coagulation disorders detected by thromboelastometry in cirrhotic patient who were candidates for invasive procedures

Correction of prohaemorrhagic clinical conditions	Ionized $Ca^{++} \geq 0.9$ mmol/l
	Hb 6–8 g/dl
	Normal haematic pH
	Antibiotic therapy if sepsis present
	Normal renal function
Substitution of coagulation factors	Fibrinogen concentrate if EXTEM or INTEM MCF reduced or CFT prolonged associated with FIBTEM MCF reduced
	Prothrombin complex only if EXTEM CT prolonged
	FFP if hyperfibrinolysis
Substitution of platelets	Platelets if EXTEM or INTEM MCF reduced or CFT prolonged associated with FIBTEM MCF normal

CFT, clot formation time; CT, clotting time; Hb, haemoglobin; FFP, fresh frozen plasma; MCF, maximum clot firmness.

patients with thrombosis (157 vs. 138%), but this difference was not statistically significant ($P = 0.147$).

Platelets adhesion and aggregation

Multiplate, PFA-100 and Light Transmission Aggregometry showed platelets adhesion or aggregation defects in 15/16 (93.8%) patients analysed. All patients had a platelet count less than 150 000/mm^3 (41 000 ± 20 710). The median haematocrit value was 29.55 ± 5.1. Bleeding events occurred only in 2/15 (13.3%) patients, with a TEM analysis showing abnormalities in clot formation depending on a qualitative or a quantitative fibrinogen defect, and not on a defect in platelet adhesion or aggregation. We should underline that 15/16 (93.8%) patients showed normal aggregation induced by ristocetin on Multiplate analysis (RISTO low test) and Light Transmission Aggregometry.

Discussion

Chronic liver disease is characterized by a complex haemostatic profile, historically considered the paradigm of acquired haemorrhagic coagulopathy and responsible for haemorrhagic diathesis in cirrhotic patients [11,19]. This paradigm changed recently: cirrhotics seem to have a balance between procoagulants and anticoagulants, resulting in a low risk of bleeding [9,11]. Moreover, the risk of bleeding may be increased with acute events such as bacterial infection, renal failure or variceal bleeding [12]. Current coagulation tests are inappropriate to predict the risk of bleeding. The lack of utility of INR in predicting the postprocedural risk of bleeding has been found in different settings such as liver biopsy [20], paracentesis [21], central venous catheter placement [22] and cardiac catheterization [23]. The platelet count can be used to predict the risk of bleeding when it is very low (under 50 000/mm^3) because of inadequate thrombin generation, but does not reflect the actual platelet functionality [24]. Despite this, INR and platelet count are still used in clinical practice and their correction is still recommended or required by different operators before an invasive procedure using an infusion of fresh frozen plasma or platelet pools [25,26].

In the setting of cirrhosis, TEM could be useful for haemostatic assessment and could aid management in case of acute haemorrhage. TEM has already been used in patients with acute variceal bleeding and during liver transplantation [27,28]. Its role in the stable cirrhosis remains debatable.

In our study, we found a low incidence of bleeding events in patients with advanced liver disease undergoing invasive procedures. Interestingly, these events also occurred in patients not considered at risk of bleeding according to conventional coagulation tests, whereas TEM identified all patients in who a bleeding complication occurred. Patients with advanced liver disease (groups A and B) have a real, even if low, risk of bleeding according to published data [29,30]. Compared with patients of group C (in whom bleeding events did not occur), patients of groups A and B showed significantly prolonged CFT (EXTEM) and abnormalities in the MCF (EXTEM, INTEM and FIBTEM). It is important to emphasize that TEM parameters, such as MCF and CFT, have a good correlation with some indexes of liver failure such as number of platelets and antithrombin III, fibrinogen and factor II levels and, unlike other parameters measured by TEM, have a low intralaboratory and interlaboratory variability [31].

Hence, abnormalities in TEM analysis have also been observed in patients with a moderate reduction in platelet number (group B). This observation is in agreement with previous data showing an important defect in platelet adhesion in cirrhotic patients [5]. In this context, TEM could identify the defect better than standard laboratory tests. It is important to underline that the risk of bleeding in this group of patients remains low (10% in our experience) despite a large number of these patients presenting an abnormal haemostatic profile according to TEM analysis. In these cases, other factors such as the type of procedure performed and the presence of comorbidities, in particular renal failure and infections, could play a role.

TEM could be useful in guiding the decision of prophylactic transfusion, enabling a focused allocation of blood products. In patients with a higher risk of bleeding (group A), TEM appears to be useful in identifying patients with a normal coagulative assessment despite severe abnormalities of INR and/or platelet count, avoiding inappropriate transfusion. In patients with mild alterations in coagulative conventional tests (group B), the decision on transfusions should be made not only on the basis of TEM results but must also consider other variables such as the type of procedure, sepsis, variceal bleeding and renal failure, which could be the real cause of the bleeding, or contribute to its worsening.

Platelet count is a better predictor of bleeding than the INR value. When it is at least 100 000/mm^3, it guarantees a normal thrombin generation [11,24]. This could explain

why all our patients with a platelet count above this threshold had a normal TEM profile despite having a pathological INR value. In clinical practice, platelet units infused before invasive procedures are usually inappropriate to significantly increase the platelet number and to improve haemostasis [32,33]. TEM helps to allocate platelets, enabling proper use and simultaneously reducing costs. Second-generation tests evaluating platelet function are very expensive and not useful in clinical practice to identify patients at risk of bleeding.

TEM showed an abnormal haemostasis caused by a deficit or an abnormality of fibrinogen in 23/58 (about 40%) patients even if fibrinogen levels are always above the transfusional threshold. Although the real impact of this fibrin polymerization defect on the risk of bleeding in cirrhotic patients remains debatable, we observed a higher frequency of fibrinogen disorders in patients who had bleeding, compared with patients who had no bleeding. This observation leads to some considerations. First, fibrinogen disorders could play a role in bleeding; therefore, its correction has to be considered before performing invasive procedures in cirrhotic patients. Second, the low incidence of haemorrhagic events in patients with fibrinogen abnormalities detected by TEM could mean that it is necessary to evaluate the presence of other risk factors, such as comorbidities or low platelet count, before transfusions. Plasma infusion has to be used with prudence, perhaps replacing it with the infusion of single coagulation factors. This substitution could avoid an increase in circulating volume and in portal pressure, reducing the potential thrombotic risk [34,35].

These observations suggest that an individual approach should be used in cirrhotic patients undergoing invasive procedures to optimize treatments and to reduce costs (see Table 6).

In our study, we observed portal thrombosis in 11/49 (22%) patients with platelet less than 100 000/mm^3 versus 2/9 (22%) patients with platelet count above this value. In these patients, TEM did not show a profile of hypercoagulability. Levels of factor VIII in these patients were not significantly higher than those of patients without portal thrombosis. This may indicate that reduced portal blood flow and endothelial damage play a prevalent role in portal vein thrombosis. In this setting, other haemostatic factors may also be important, as shown by our experience in the multicentric study (ELEVATE): among our patients treated with eltrombopag, a thrombopoietic agent, only patients with prothrombin mutation and protein C deficiency developed thrombotic events [36]. In conclusion, in the complex scenario of the haemostatic profile in patients with cirrhosis, the preventive and indiscriminate use of a large amount of blood products is no longer justified and an individual approach must be used. Our observations, even though preliminary and limited to a single experience, support the use of TEM analysis for a more optimal clinical management of cirrhotic patients. Large randomized-controlled trials are urgently needed to organize and standardize all available data in this field.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Tripodi A, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, *et al*. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology* 2009; 137:2105–2111.

2 Witters P, Freson K, Verslype C, Peerlinck K, Hoylaerts M, Nevens F, *et al*. Review article: blood platelet number and function in chronic liver disease and cirrhosis. *Aliment Pharmacol Ther* 2008; 27:1017–1029.

3 Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. *Aliment Pharmacol Ther* 2007; 26 (Suppl 1):13–19.

4 Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, *et al*. Thrombocytopenia associated with chronic liver disease. *J Hepatol* 2008; 48:1000–1007.

5 Ordinas A, Escolar G, Cirera I, Viñas M, Cobo F, Bosch J, *et al*. Existence of a platelet-adhesion defect in patients with cirrhosis independent of hematocrit: studies under flow conditions. *Hepatology* 1996; 24:1137–1142.

6 Tripodi A, Anstee QM, Sogaard KK, Primignani M, Valla DC. Hypercoagulability in cirrhosis: causes and consequences. *J Thromb Haemost* 2011; 9:1713–1723.

7 Tripodi A, Mannucci PM. Abnormalities of hemostasis in chronic liver disease: reappraisal of their clinical significance and need for clinical and laboratory research. *J Hepatol* 2007; 46:727–733.

8 Kinjo N, Kawanaka H, Akahoshi T, Matsumoto Y, Kamori M, Nagao Y, *et al*. Portal vein thrombosis in liver cirrhosis. *World J Hepatol* 2014; 6:64–71.

9 Tripodi A. The coagulopathy of chronic liver disease: is there a causal relationship with bleeding? No. *Eur J Intern Med* 2010; 21:65–69.

10 Lisman T, Bongers TN, Adelmeijer J, Janssen HL, de Maat MP, de Groot PG, Leebeek FW. Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity. *Hepatology* 2006; 44:53–61.

11 Tripodi A, Primignani M, Mannucci PM. Abnormalities of hemostasis and bleeding in chronic liver disease: the paradigm is changed. *Intern Emerg Med* 2010; 5:7–12.

12 Montalto P, Vlachogiannakos J, Cox DJ, Pastacaldi S, Patch D, Burroughs AK. Bacterial infection in cirrhosis impairs coagulation by a heparin effect: a prospective study. *J Hepatol* 2002; 37:463–470.

13 Whiting D, DiNardo JA. TEG and ROTEM: technology and clinical applications. *Am J Hematol* 2014; 89:228–232.

14 Tripodi A, Primignani M, Chantarangkul V, Viscardi Y, Del'Era A, Fabris FM, Mannucci PM. The coagulopathy of cirrhosis assessed by thromboelastometry and its correlation with conventional coagulation parameters. *Thromb Res* 2009; 124:132–136.

15 Stravitz RT. Potential applications of thromboelastography in patients with acute and chronic liver disease. *Gastroenterol Hepatol (N Y)* 2012; 8:513–520.

16 Johansson PI, Stissing T, Bochsen L, Ostrowski SR. Thrombelastography and tromboelastometry in assessing coagulopathy in trauma. *Scand J Trauma Resusc Emerg Med* 2009; 17:45.

17 Guidelines on Plasma Transfusion; City of the Health and Science, Turin, Italy. Available at: *http://www.cittadellasalute.to.it/images/stories/MOLINETTE/area_documentale/linee_guida/trasfusione_plasma.pdf*. [Accessed 1 February 2014].

18 Guidelines on Platelets Transfusion; City of the Health and Science, Turin, Italy. Available at: *http://www.cittadellasalute.to.it/images/stories/MOLINETTE/area_documentale/linee_guida/LG_PLTS_aggiornamento-marzo-13.pdf*. [Accessed 1 February 2014].

19 Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, *et al*. Hemostasis and thrombosis in patients with liver disease: the up and downs. *J Hepatol* 2010; 53:362–371.

20 Rockey DC, Caldwell SH, Goodman ZD, Nelson SC, Smith AD. American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology* 2009; 49:1017–1044.

21 Grabau CM, Crago SF, Hoff LK, Simon JA, Melton CA, Ott BJ, Kamath PS. Performance standards for therapeutic abdominal paracentesis. *Hepatology* 2004; 40:484–488.

22 Segal JB, Dzik WH. Transfusion Medicine/Hemostasis Clinical Trials Network. Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review. *Transfusion* 2005; 45:1413–1425.
23 Townsend JC, Heard R, Powers ER, Reuben A. Usefulness of international normalized ratio to predict bleeding complications in patients with end-stage liver disease who undergo cardiac catheterization. *Am J Cardiol* 2012; 110:1062–1065.
24 Giannini EG. Platelet count manipulation and modification of global haemostasis tests in patients with chronic liver disease: almost there, almost there**…**. *Liver Int* 2013; 33:325–326.
25 Coêlho GR, Feitosa Neto BA, de G Teixeira CC, Marinho DS, Rangel ML, Garcia JH. Single-center transfusion rate for 555 consecutive liver transplantations: impact of two eras. *Transplant Proc* 2013; 45:3305–3309.
26 Patel IJ, Davidson JC, Nikolic B, Salazar GM, Schwartzberg MS, Walker TG, Saad WA. Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. *J Vasc Interv Radiol* 2012; 23:727–736.
27 Massicotte L, Beaulieu D, Thibeault L, Roy JD, Marleau D, Lapointe R, *et al*. Coagulation defects do not predict blood product requirements during liver transplantation. *Transplantation* 2008; 85:956–962.
28 Weeder PD, Porte RJ, Lisman T. Hemostasis in liver disease: implications of new concepts for perioperative management. *Transfus Med Rev* 2014; 28:107–113.
29 Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequence. *Blood* 2010; 116:878–885.
30 Caldwell S, Shah N. The prothrombin time-derived international normalized ratio: great for warfarin, fair for prognosis and bad for liver-bleeding risk. *Liver Int* 2008; 28:1325–1327.
31 Chitlur M, Sorensen B, Rivard GE, Young G, Ingerslev J, Othman M, *et al*. Standardization of thromboelastography: a report from the TEG-ROTEM working group. *Haemophilia* 2011; 17:532–537.
32 Giannini EG. Thrombocytopenia in patients with chronic liver disease: what's in a name? *Dig Dis Sci* 2013; 58:299–301.
33 Tripodi A, Primignani M, Chantarangkul V, Lemma L, Jovani M, Rebulla P, Mannucci PM. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. *Liver Int* 2013; 33:362–367.
34 Youssef WI, Salazar F, Dasarathy S, Beddow T, Mullen KD. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. *Am J Gastroenterol* 2003; 98:1391–1394.
35 Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013; 11:1064–1074.
36 Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, *et al*. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med* 2012; 367:716–724.