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Original paper

The procedure-related bleeding rate in advanced chronic liver disease does not increase without pre-emptive use of prothrombin complex concentrates

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Abstract

Introduction: Procedure-related bleeding (PRB) in patients with liver cirrhosis (advanced chronic liver disease – ACLD) is a serious problem. The standard protocol (SP) for prevention of PRB usually consists of three steps: 1) consultation of a hematologist before the procedure; 2) standard panel of *in vitro* hemocoagulation tests (HT); 3) preemptive hematological therapy based on results of these tests and calculated by the hematologist. In step 3, hemocoagulation factors (HF) are administered with the intent to correct abnormalities in HT. The understanding of hemostasis in ACLD has changed in recent years, however. It is believed, that: i) the hemostatic balance is re-set to equilibrium (albeit fragile), or even to a slight pro-coagulant state; ii) standard HT have questionable (if any) role in guiding the prevention of PRB; iii) administering HF prophylactically based on the results of HT does not decrease the rate of PRB, and may lead to an increase in portal hypertension, serious adverse events and considerable cost. Therefore, authorities have discouraged universal use of HF based on the results of HT (i.e. omission of step 3); instead, they advised on either watchful waiting with HF administered only on demand (in cases of PRB), or using HF based on new generation HT such as thromboelastometry. Aim of the study was to compare the rates of PRB between two groups of patients with ACLD: those managed according to 3-step SP (group A), to the 2-step so-called modified protocol (MP, group B).

Material and methods: Retrospective study. Analysis of charts from the hospital information system database. Group A (SP): consecutive patients admitted between January 1st, 2011 and August 31st, 2012; these patients were administered full doses of HF as calculated by the hematologist based on HT (step 3) before procedures. Group B (MP, the omission of step 3): consecutive patients hospitalized between September 1st, 2012 and December 31st, 2013; HF were administered only in cases of PRB. The whole cohort consisted of consecutive patients referred to consider LTx candidacy. Inclusion criteria: ACLD considered as an indication for LTx; requirement of the invasive procedure according to pre-LTx protocol. Recorded variables: gender, etiology of ACLD, Model of end-stage liver disease (MELD), Child-Pugh score, prothrombin time, INR, platelet count, aPTT, fibrinogen, PRB, use of HF.

Results: PRB was recorded in 23% of patients from SP and in 21% from MP (ns). The average expenditures per patient in Group A and B were €536.58 and €384.53 ($p = 0.02$), resulting in overall savings of €152 per patient.

Conclusions: In patients with ACLD considered for LTx, withholding HF before procedures did not increase the rate of PRB and led to considerable cost savings.

Key words: liver cirrhosis, coagulation, bleeding, thrombosis, invasive procedures.

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Introduction

The standard approach to coagulation in liver cirrhosis

Cirrhosis (advanced chronic liver disease – ACLD) has been commonly perceived as a prototypical acquired bleeding disorder (coagulopathy), brought about by decreased synthesis of procoagulant factors, the extent of which is reflected in prolongation of standard coagulation tests (standard tests – i.e., prothrombin time [PT], international normalized ratio [INR], and activated partial thromboplastin time [aPTT]) [1-5]. This perception has led to the use of pre-procedural transfusions of agents (fresh-frozen plasma [FFP], prothrombin complex concentrates [PCC], antifibrinolytic drugs, recombinant f. VII, antithrombin III [AT] and fibrinogen [FBG], etc.) to improve coagulation tests and prevent procedure-related bleeding (PRB) [2, 6-8].

The standard approach revisited

Recently, however, evidence has been provided that supports the view of hemostasis in ACLD as the new state of balance. This balance is fragile and characterized by a concomitant reduction in the synthesis of both procoagulants and anticoagulants; the fragility of the balance is further increased by thrombocytopenia or thrombocytopathy. It has also been shown that standard tests without thrombomodulin are rarely predictive of the risk of bleeding [4, 5, 9-16]. Therefore, new assays capable of globally assessing clotting function are being investigated – such as thrombin generation and thromboelastography [10, 17]. Furthermore, there is evidence to suggest an even more counterintuitive notion – that the hemostatic balance in ACLD has been tilted towards hypercoagulability, with serious clinical consequences [4, 5, 10, 15, 16, 18-23]. The cause is that many pro-hemostatic drivers are relatively increased (von Willebrand factor, factor VIII), and anticoagulants decreased (protein C, protein S, antithrombin, ADAMTS-13) [4, 5, 24-28]. The answer to the remaining question of why patients with ACLD bleed may primarily lie beyond the realm of hemostasis, namely in portal hypertension, endothelial dysfunction, bacterial infections, and uremia [4, 5, 29]. Only platelet (PLT) deficit has been linked to the risk of bleeding and should therefore always be corrected, although the association is also weaker than expected [30].

The modified approach

As a consequence of the above, it has been suggested that the standard approach be replaced with a modified one. Not only have standard tests been declared unsuitable for assessing hemorrhagic risk, but the positive impact of pre-emptive infusions of FFP and procoagulant factors such as PCC, AT and FBG has also been questioned [4, 5]. Signals arose from the change in the pathophysiological paradigm, negative results of interventional studies and evidence of potential harm brought on by preoperative transfusions [2, 4, 5, 15, 16, 31-34]. Clinically, the most harmful consequence of the standard approach has been the worsening of portal hypertension, which is the main driver of bleeding: 250 ml of FFP increases the INR by 0.1, but portal pressure by 1 mm Hg [35, 36]. Therefore, authorities advise against the routine use of transfusions to correct deviations in standard tests before invasive procedures. Instead, they recommend transfusions based on the results of new assays, or on-demand transfusions, given only in cases of clinically significant procedure-related bleeding (PRB) [2, 10, 37, 38].

At the HEGITO, the transition from the standard to the modified approach was made in September 2012. At that time, new assays were not available. We conceived this study as a quality control assessment and pragmatic trial [39, 40].

Aim of the study was to investigate the frequency of procedure-related bleeding (PRB) in patients with decompensated (d) ACLD, specifically candidates for liver transplant (LTx). Also, to compare the outcome between two cohorts: Group A, in which we used a standard approach to prevention of PRB, and Group B, in which we introduced a modified approach. We hypothesized that the modified approach would not lead to an increased incidence of PRB and would reduce financial costs.

Material and methods

We conducted this retrospective study by analysis of charts from the hospital information system database (CareCenter, Copyright 2000, CMG, version 3.10.1), analyzed by one investigator (PM). Group A (controls, standard approach) consisted of consecutive patients admitted to HEGITO with dACLD between January 1, 2011, and August 31, 2012. In group B (cases, modified approach) we enrolled consecutive patients admitted with dACLD between September 1, 2012, and December 31, 2013. Our site was the Liver Unit with an LTx program. Inclusion criteria: We enrolled adult patients with dACLD on admission who were potential candidates for LTx and were in need to undergo a procedure of low to medium invasiveness [41] (Table 1). All the patients provided informed consent. Exclusion criteria: we excluded patients who declined informed consent, who had a bleeding tendency as determined by the patient's medical history and objective examina-

Table 1. Types of invasive procedures and frequency of procedure-related bleeding

Intervention	Group A		Group B		*p*
	n (%)	Bleeding, *n* (%)	*n* (%)	Bleeding, *n* (%)	Bleeding, *n* (%)
Dentistry – dental extractions	10 (16)	3 (30)	6 (14)	1 (17)	NS
Laparoscopy with abdominal hernia repair	8 (13)	0 (0)	7 (16)	1 (11)	NS
HVPG measurement	8 (13)	3 (38)	4 (9)	0 (0)	NS
Cannulation of the central vein	7 (11)	1 (14)	7 (16)	4 (57)	NS
Liver biopsy	7 (11)	1 (14)	3 (7)	1 (33)	NS
Paracentesis of ascites	7 (11)	0 (0)	2 (5)	0 (0)	NS
TIPS	7 (11)	2 (29)	5 (12)	2 (40)	NS
Endoscopic polypectomy	3 (6)	1 (33)	5 (12)	0 (0)	NS
EVBL	1 (2)	1 (100)	1 (2)	0 (0)	NS
ERCP	1 (2)	1 (100)	–	–	–
Thoracentesis (fluidothorax)	1 (2)	0 (0)	–	–	–
TACE	1 (2)	1 (100)	–	–	–
RFA	–	–	2 (5)	0 (0)	–
Upper GI endoscopy with biopsy	–	–	1 (2)	0 (0)	–

TIPS – transjugular intrahepatic portosystemic shunt, EVBL – endoscopic variceal band ligation, ERCP – endoscopic retrograde cholangiopancreatography, TACE – transarterial chemoembolization, RFA – radiofrequency ablation

tion. We also excluded patients with malignancy apart from HCC in Milan criteria.

The standard approach (used until September 2012) consisted of the following steps: 1. Indication of invasive procedure grade < 3 [41]; 2. Prescription of transfusions by a hematologist – in doses calculated based on standard tests; 3. Transfusions of the full recommended doses of FFP, PCC, AT, etc., before the invasive procedure; 4. Invasive procedure; 5. Follow-up. Modified approach (used from September 1, 2012 onward) was characterized by the omission of step three. Specifically, transfusions were available but were administered only in cases of PRB. The list of invasive procedures (Table 1) consisted of: cannulation of the central veins, dental surgery, transjugular intrahepatic portosystemic shunt (TIPS), insertion of a peritoneal catheter, laparoscopy with umbilical hernia repair, measurement of the hepatic venous pressure gradient (HVPG), transjugular liver biopsy (TJLB), gastrointestinal endoscopic biopsy or polypectomy, endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, transarterial chemoembolization (TACE), radiofrequency ablation (RFA).

The primary endpoint was the frequency of PRB, defined as apparent bleeding, or a decrease in hemoglobinemia of at least 0.5 g/l immediately, or up to 7 days after the procedure. Secondary endpoints were: new thrombosis; death; transfusions of erythrocytes, FFP, PCC, AT; length of hospital stay (LOS), costs of both approaches.

Recorded variables are listed in Table 2. We considered the differences between outcomes as statistically significant if $p < 0.05$. The Institutional Ethics Committee has approved the study.

Results

We recorded a total of 104 cases, in 72 of which (69%) the patients were male. The mean age was 50.4 years (21–67). The etiology of decompensated ACLD was alcoholic liver disease (ALD) in 50 cases (48%), viral hepatitis in 12 (11%) [7 (6.5%) with hepatitis B (HBV) and 5 (4.5%) with hepatitis C (HCV)], non-alcoholic steatohepatitis (NASH) in 11 (10.5%), autoimmune hepatitis (AIH) in 7 (7%), primary sclerosing cholangitis (PSC) in 8 (8%), primary biliary cholangitis (PBC) in 3 (3%), cryptogenic in 12 (11.5%). The average Child-Pugh score was 9 points (5–13), and the model for end-stage liver disease (MELD) 16 (8–34) (Table 2).

We enrolled 61 patients in group A and 43 patients in group B (Fig. 1). There were 14 episodes of PRB in group A (23%) and 9 in group B (21%) ($p = 0.809$) (Figs. 1-2, Table 3). The incidence of clinically evident thrombotic episodes (group A = 10, group B = 7) and deaths (12 and 5, respectively) did not significantly differ between the groups (Table 3).

Table 2. Baseline characteristics

Factor	Group A (*n* = 61)		Group B (*n* = 43)		*p*
	n	%	*n*	%	
Age (years)	52	–	48	–	0.029
Gender					
Male	41	67	31	72	NS
Female	20	33	12	28	NS
Aetiology of chronic liver disease (cirrhosis)					
ALD	31	51	19	44	NS
NASH	3	5	8	18	0.025
HBV	4	6.5	3	7	NS
HCV	5	8	0	0	NS
PSC	6	10	2	4.7	NS
AIH	6	10	1	2.3	NS
PBC	2	3	1	2.3	NS
Cryptogenic	4	6.5	8	18	NS
Other	0	0	1	2.3	NS
Prognostic scoring and laboratory parameters					
Ascites	33	54	25	58	NS
Child-Pugh score (points)	9	–	9	–	NS
MELD score (points)	15	–	18	–	0.002
Bilirubin (µmol/l)	108	–	133	–	NS
Creatinine (µmol/l)	86	–	104	–	0.026
Albumin (g/l)	30	–	29	–	NS
INR	1.45	–	1.62	–	0.038
PT (%)	55	–	48.6	–	0.015
aPTT (s)	43	–	48.9	–	0.021
Fibrinogen (g/l)	3.1	–	2.8	–	NS
Thrombin time (s)	25	–	30	–	0.038
Antithrombin III (%)	56.4	–	47	–	NS
Platelets (10^9/l)	137	–	116	–	NS

ALD – alcoholic liver disease, NASH – non-alcoholic steatohepatitis, HBV – hepatitis B virus, HCV – hepatitis C virus, PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis, PBC – primary biliary cholangitis, MELD – Model for End Stage Liver Disease, PT – prothrombin time, INR – international normalized ratio, aPTT – activated partial thromboplastin time

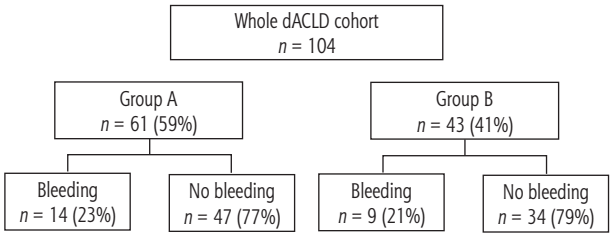

Fig. 1. Flowchart

When we looked more closely at the specific invasive procedures, there were no statistically significant differences between group A and group B in PRB associated with any particular invasive procedure; the range of procedures and relative frequency of PRB are depict-

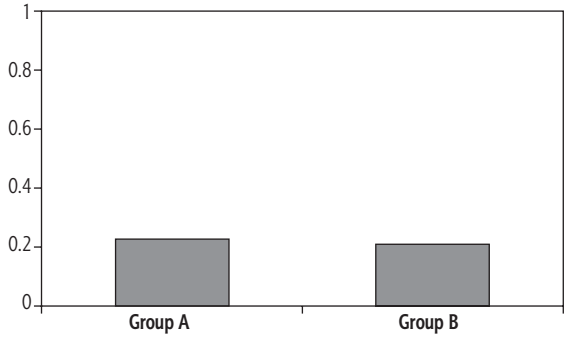

Fig. 2. Incidence of procedure-related bleeding according to the type of approach. Standard approach = group A, modified approach = group B (*p* = NS)

Table 3. Results 1: Summary of main outcomes

Factor	Group A		Group B		*p*
	61		43		
	n	%	*n*	%	
Bleeding	14	23	9	21	NS
Thrombosis	10	16	7	16	NS
Mortality	12	20	5	12	NS

ed in Table 1. There was a significant reduction in the use of PCC and overall cost per patient in group B as compared to group A, a significant increase in the use of hemostatic agents (such as etamsylate) in group B, and no difference in the use of other transfusions, including FFP (Table 4, Fig. 3). The average expenditures per patient in groups A and B were €536.58 and €384.53, respectively (p = 0.02), resulting in overall savings per patient in group B of €152. Savings for the most expensive factors – PCC, AT and FBG – reached €239.19.

Discussion

The main finding of this study relates to the safety of the modified approach as measured by the frequency of PRB. One in five patients experienced bleeding, irrespective of whether pre-operative transfusions were administered or withheld. These results lend further support to accumulating evidence suggesting i) hemostatic equilibrium in dACLD, ii) the inability of standard tests to predict bleeding, and iii) futility of correction of abnormalities found by standard tests. In this regard, the study can be considered a pragmatic trial [39, 40].

There are two essential conditions to ensure the safety of the modified approach: 1) the selection of appropriate patients and 2) selection of appropriate invasive procedures. As regards patients with dACLD, they should always be selected for the modified approach only after the consensus of the hematologist with the attending hepatologist (only patients with no evidence of bleeding tendencies based on their medical histories and objective examination are eligible). It is no less critical that the invasive procedures selected for the modified approach should be of low-to-medium invasiveness; simply put, the character of the procedure should enable PRB to be halted by mechanical compression or interventional radiology, without the need for major surgery. All of the procedures used in the study (Table 2) meet this condition with the exception of percutaneous liver biopsy, which should be selected for the modified approach with great caution. When these conditions are fulfilled, prophylactic transfusions of clotting factors to correct deviations

Table 4. Results 2: Secondary endpoints – use of transfusions, financial expenses

Factor	Group A	Group B	*p*
Fresh frozen plasma	3.6	5.0	0.089
Vitamin K	1.8	1.6	0.342
PAMBA	0.4	0.8	0.027
Etamsylate	0.7	1.9	0.006
Prothrombin complex concentrate 1	0.54	0.14	0.023
Prothrombin complex concentrate 2	0.34	0.07	0.031
Antithrombin III	0.11	0	0.126
Fibrinogen	0.11	0.05	0.167
Packed red blood cells	0.93	1.63	0.096
Platelets	0.15	0.16	0.443
Overall cost of hematological preparations (€ patient)	536.58	384.53	0.02

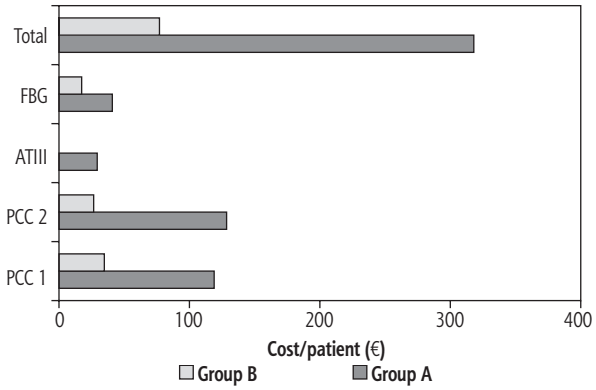

Fig. 3. Comparison of expenditures (€ per patient) for therapy with coagulation factor concentrates. Group A = standard approach, group B = modified approach. FBG – fibrinogen, ATIII – antithrombin, PCC – prothrombin complex concentrate

in standard tests should be reconsidered and could be withheld without increasing the risk of PRB.

The study results clearly show that the modified approach leads to considerable savings – mostly provided through the reduced use of the most expensive factors, such as PCC, AT, and FBG. The savings could have been even higher if the restrictive strategy in the modified approach had also included FFP. Since the quantity of FFP transfusions in the study was not different between the two groups, we conclude that there may still be room for improvement in the modified approach. It is widely accepted and has been frequently observed that the increase in portal pressure induced by the volume effect of FFP far outweighs the modest benefit provided by clotting factors, with an overall net increase in bleeding risk. Therefore, reducing FFP should be the next step in the evolution of the modified approach. Similarly, the use of adjuvant hemostatic drugs (called hemostyptics

in Slovakia), which were overused in group B due to unknown reasons, should be discouraged. It is possible that the attending physicians felt the urge to somehow compensate for not providing clotting factors; the real reasons could be mediated by the risk-aversive environment and defensive medicine. These reservations notwithstanding, the modified approach has already proved its potential to save considerable resources without increasing the risk of PRB.

The study has several limitations. The retrospective design could affect all the domains. We believe that most influenced might be the data on the availability of transfusions since their recording was left at the discretion of attending physicians. Other inputs were delivered to the database automatically (i.e., from laboratories). Even if operative, their influence on the results is considered minor due to their symmetrical distribution between the two groups. The limited sample size could have caused small disparities in the baseline characteristics (MELD, NASH, age, PT, etc.), but their impact on the results would be mitigating, not emphasizing the differences between groups; therefore, we do not think they threaten the conclusions.

In conclusion, the adoption of the modified approach in patients in the most advanced stages of ACLD and under consideration for LTx is safe and leads to considerable economic benefit.

Conclusions

In patients with ACLD considered for LTx, withholding HF before procedures did not increase the rate of PRB and led to considerable cost savings.

Disclosure

Authors report no conflict of interest.

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