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# PROCEDURE-RELATED BLEEDING IN ADVANCED CHRONIC LIVER DISEASE DOES NOT INCREASE WITHOUT PRE-EMPTIVE USE OF PROTHROMBIN COMPLEX CONCENTRATES.

Medicine

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## KEYWORDS

### A. BACKGROUND

A.1.Standard approach. Cirrhosis (Advanced Chronic Liver Disease, ACLD) has been commonly perceived as a A.1.a) prototypical acquired bleeding disorder (coagulopathy) A.1.b) brought about by decreased synthesis of procoagulant factors, the extent of which is A.1.c) reflected in prolongation of standard coagulation tests (standard tests) – i.e., prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). (2, 22, 29, 34, 35). This perception has led to the use of A.1.d) 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) (17, 20, 22, 39).

A.2.Standard approach revisited. Recently, however, evidence has been provided that supports the view of haemostasis in ACLD as the A.2.a) new state of fragile balance A.2.b) characterized by a concomitant reduction in the synthesis of both procoagulants and anticoagulants, further weakened by thrombocytopenia (but still in equilibrium) or thrombocytopathy; it has also been shown that A.2.c) standard tests without thrombomodulin are rarely predictive of the risk of bleeding (3, 7, 13, 23, 28, 30, 31, 32, 34, 35). Therefore, new assays capable of globally assessing clotting function are being investigated – such as thrombin generation and thromboelastography(7, 24). Furthermore, there is evidence to suggest an even more counterintuitive notion – that the haemostatic balance in ACLD has been tilted towards A.2.d) hypercoaguability), with serious clinical consequences (7, 10, 15, 16, 19, 27, 31, 32, 34, 35, 37). The cause is that many pro-haemostatic drivers are relatively increased (von Willebrand factor, factor VIII) and anticoagulants decreased (protein C, protein S, antithrombin, ADAMTS-13)(1, 8, 14, 34, 35, 36, 38). The answer to the remaining question of why patients with ACLD bleed may primarily lie beyond the realm of haemostasis: namely in portal hypertension, endothelial dysfunction, bacterial infections, and uraemia (6, 34, 35). Only platelet (PLT) deficit shave been linked to the risk of bleeding and should therefore always be corrected, although the association is also weaker than expected (12).

A.3. Modified approach. As a consequence of A.2., particularly A.2.c), it has been suggested that the standard approach (A.1.d)be replaced with a modified one. Not only have standard tests been declared unsuitable for assessing haemorrhagic risk, but the positive impact of pre-emptive infusions of FFP and procoagulant factors such as PCC, AT and FBG have also been questioned (34, 35). Signals arose from the a)change in the pathophysiological paradigm, b)negative results of interventional studies, and c)evidence of potential harm brought on by preoperative transfusions (4, 5, 18, 21, 22, 31, 32, 34, 35). Clinically, the most deleterious consequence of the standard approach has been worsened 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 (33, 40). Therefore, authorities advise against the routine use of transfusions to correct deviations in standard tests before invasive procedures and instead recommendA.3.i) transfusions based on the results of new assays (A.2.c), or A.3.ii) on-demand transfusions, given only in cases of clinically significant procedure-related bleeding (PRB) (7, 22, 26, 41).

At HEGITO, the transition from standard A.1. d) to the modified approach in subtype A.3. ii) was made in September 2012.At that time, new assays were not available, therefore approach subtype A.3.i) was not considered. This study has been conceived as a quality-control assessment and pragmatic trial (9, 25).

### B. AIM

The aims of the study were to investigate the frequency of procedure-related bleeding (PRB) in patients with decompensated (d) ACLD, specifically candidates for liver transplant (LTx), and to compare the outcomes in two cohorts: Group A, in which there was a standard approach to prophylaxis for PRB, and Group B, which had a modified approach. The hypothesis was that the modified approach would not lead to an increased incidence of PRB and would lead to reduced financial costs.

### C. PATIENTS AND METHODS

Retrospective study. Analysis of charts from the hospital information system database (CareCenter, Copyright 2000, CMG, version 3.10.1), analysed by one investigator–PM. Group A (controls, standard approach): consecutive patients admitted to HEGITO between 1 January2011 and 31 August 2012; Group B (cases, modified approach):consecutive patients admitted between 1 September2012 and 31 December2013. Site: Liver Unit with a liver transplant programme. Inclusion criteria: Adult; decompensated ACLD on admission; potential candidate for LTx; clinical need to perform a procedure of low-to-medium invasiveness (11)(Table 1); informed consent. Exclusion criteria: declined informed consent; bleeding tendency as determined from the patient's medical history and objective examination; malignancy; lack of data for final analysis. Standard approach (used until September 2012): 1. Indication of invasive procedure grade < 3 (11); 2. Prescription of transfusions by a haematologist – in doses calculated based on standard tests (A.1.c); 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): Omission of step 3.,i.e., transfusions were available but only administered in cases of PRB. Invasive procedures (Table 1): 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).

Primary endpoint: Frequency of PRB, defined as apparent bleeding, or a decrease in haemoglobinaemia of at least 0.5 g/l immediately, or up to 7 days post-procedure. Secondary endpoints: a)new thrombosis; b)death; c)transfusions of: erythrocytes, FFP, PCC, AT; d) length of hospital stay (LOS), e)costs of both approaches. Recorded variables: (Table 2). Differences between the outcomes were considered statistically significant if $p < 0.05$. The study has been approved by the local Ethics Committee.

## D. RESULTS

A total of 104 cases were recorded, 72 of which (69%) were males. The mean age was 50.4 years (21–67) . The aetiology 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).

Sixty-one patients were enrolled in Group A and 43 patients in Group B (Graph 1). There were 14 episodes of PRB in Group A (23%) and 9 in Group B (21%) ($p = 0.809$) (Graph 1, Graph 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).

Upon closer look at the individual 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 depicted 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 haemostatic agents (such as etamsylate) in Group B, and no difference in the use of other transfusions, including FFP (Table 4, Graph 3). The average expenditures per patient in Group 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.

## E.DISCUSSION

The main finding of this study related 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 have lent further support to accumulating evidence suggesting i)haemostatic equilibrium in decompensated ACLD, ii)inability of standard tests to predict bleeding, and iii)futility of correcting abnormalities found in standard tests. In this regard, the study can be considered a pragmatic trial (9, 25).

There are two crucial conditions which must not be played down to ensure the safety of the modified approach: the selection of appropriate patients and selection of appropriate invasive procedures. As regards patients with decompensated ACLD, they should always be selected for the modified approach only following the consensus of the haematologist and attending hepatologist (only patients with no evidence of bleeding tendencies based on their medical histories and objective examination are eligible). It is no less important to underscore that the type of invasive procedure in which the modified approach can be used with sufficient safety should be of low-to-medium invasiveness; simply put, the character of the procedure should enable PRB to be halted through 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 modified approach with great caution.

When these conditions are fulfilled, prophylactic transfusions of clotting factors to correct deviations in standard tests should be reconsidered and could be withheld without increasing the risk of PRB.

The study results clearly show that this 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, however, if the restrictive strategy in the modified approach would have also included FFP. Since the quantity of FFP transfusions in the study was no different between the two groups, we concluded 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, use of adjuvant haemostatic drugs (called haemostyptics 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 true reasons could be behavioural or 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. Its retrospective design could affect all fields; however, the authors believe that the collection of data concerning transfusion availability may be influenced most, since the recording of this data was 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 the even distribution over 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, the conclusions are not considered threatened.

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.