

POSITION

by Prof. Fani Georgieva Martinova, MD, PhD, DSc

Laboratory of Transfusion Hematology

UMHATEM „N. I. Pirogov ”EAD - Sofia

Regarding dissertation "Rotational thrombelastometry as a method for assessing hemostasis changes and the risk of varicose bleeding in patients with liver cirrhosis"

of Kamen Valentinov Danov MD

for awarding the educational and scientific degree "Doctor"

in the scientific specialty "Internal Medicine",

in a professional direction 7.1. Medicine in the field of higher education

7. Health and sports

Patients with severe liver disease, such as cirrhosis or acute liver failure, often have haemorrhagic diathesis, thrombocytopenia and portal hypertension, and these changes are different in acute and chronic conditions. Hemostasis in its three phases (primary hemostasis, coagulation and fibrinolysis) is affected by liver disease. In patients with cirrhosis, primary hemostasis is considered impaired due to platelet dysfunction and thrombocytopenia, the coagulation phase is also impaired, and these patients are in a state of hypercoagulation rather than a tendency of bleeding. This is due to increased levels of factor VIII and von Willebrand factor (vWF), endothelial activation, decreased levels of protein C from reduced hepatic synthesis and possibly increased consumption. Finally, the clot resorption phase in hemostasis is considered to be impaired in patients with cirrhosis due to decreased levels of profibrinolytic proteins.

Standard coagulation assays, PT / INR or aPTT, assess only plasma events in haemostasis, omitting platelet clot formation as well as interactions with other cellular components of the blood. Therefore, INR and aPTT are not informative

and may provide an inadequate and possibly misleading assessment of the risk of bleeding in patients with liver disease.

The dissertation of Kamen Danov MD is a topical and important for medical science and practice problem related to the application of rotational thromboelastometry (ROTEM), as a modern concept for balanced hemostasis in patients with liver cirrhosis and portal hypertension, to assess changes in overall hemostasis and risk assessment of varicose bleeding in these patients.

The dissertation is presented on 198 pages, illustrated with 91 tables and 60 figures. It is structured according to the requirements for dissertation work.

In a purposeful and comprehensive literature review, Dr. Kamen Danov presents literature data on the changes, features and diagnosis of hemostasis in patients with liver cirrhosis. Modern theories on the causes of varicose bleeding, structural and functional changes and factors in the pathogenesis of portal hypertension, features of hemostasis in liver disease, the principles of global methods for monitoring coagulation, the principles and parameters of rotational thrombelastometry, conventional coagulation methods, data on the practical application of thrombelastometry in liver cirrhosis are reviewed.

The cited literature covers 254 titles, of which 249 in English and 5 in Bulgarian. The review is from current literature sources (36% are from the last 10 years) and testifies to the excellent awareness of the doctoral student about the issues under consideration.

The aim of the dissertation is clearly formulated - to study the applicability of the method of rotational thrombelastometry to assess hemostatic changes and the risk of varicose bleeding in patients with liver cirrhosis and portal hypertension.

The tasks for achieving the aim are 5, they are defined precisely and logically and are related to the main aim. These include a study in patients with cirrhosis of the liver with and without varicose bleeding and a comparison of individual ROTEM parameters, a comparison of ROTEM parameters with those of conventional coagulation tests, a study of the diagnostic value of ROTEM and the development of a diagnostic algorithm to assess the risk of bleeding in patients with liver cirrhosis.

The clinical contingent includes 108 patients aged 39 to 69 years, 91 men and 17 women. Patients were divided into 3 groups: 55 patients with cirrhosis of the liver and bleeding from esophageal varices, 29 patients with cirrhosis without

bleeding from esophageal varices and 24 patients without liver pathology as a control group.

The research methods are hematological methods for assessment of FBT (number of blood cells, Hb and Ht), biochemical methods for assessment of the severity of liver cirrhosis (ALAT, ASAT, GGT, AF, CRP), methods for examination of hemostasis: conventional methods for the study of Fibrinogen, PTT, INR and the method of rotational thrombelastometry with automatic analyzer ROTEM Sigma and statistical methods with statistical package IBM SPSS for data entry and processing.

The tests by ROTEM were performed in 4 panels: EXTEM (activation of the external system and the common coagulation pathway); INTEM (activation of the internal system and the common coagulation pathway); FIBTEM (suppression of platelet function to assess fibrinogen / fibrin in clot formation); HEPTTEM (assessment of the presence of heparin). Coagulation time (CT), clot formation time (CFT); maximum clot strength (MCF), indicators were monitored thrombodynamic potential index (TPI) was calculated.

Own results include:

1. Study of conventional hemostasis tests (PT sec., PT%, INR, aPTT) and their distribution among patients in the three groups and by sex. The highest values of INR are found in groups I and II, and of aPTT - in group II, without bleeding.
 2. Platelet count test - the lowest values are found in patients of group I with bleeding, more often in women.
 3. Tests for inflammatory activity (number of leukocytes, CRP) - the number of leukocytes does not show a significant increase or deviation in the three groups; serum CRP levels are elevated in group I.
 4. INTEM parameters: 1) CT and CFT do not show a significant difference between group I and group II, but differ significantly from the control group, especially group I with bleeding; 2) TPI shows a significant association with the presence of bleeding episodes in liver cirrhosis; 3) in control group III there are no coagulation disorders and TPI in ROTEM is comparable on a case-by-case basis due to the absence of liver pathology.
 5. EXTEM parameters: there are significant changes in the values of CT, CFT and TPI; 1) in group I there are two tendencies - for impaired coagulation and
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for hypercoagulation; 2) TPI significance in group II, without bleeding; 3) TPI with high sensitivity and lower specificity for control group III, without liver pathology and serves as a reference group.

6. Parameters of FIBTEM: there is a tendency to pronounced fibrinolysis or disturbed fibrinolysis, significant differences in the 5 evaluation indicators; significant difference for group I with bleeding, compared with group II and control; CT shows the widest range of values in group I and confirms that there is a state of hypercoagulation with impaired fibrinolysis or a state of hypocoagulation with impaired fibrinolysis.

7. Parameters of HEPTM: there is a significant difference in the activity of this panel and the heterogeneity of coagulation disorders in patients with bleeding group I; strongly increased and a significant number of decreased values are of CT and CFT.

8. Study of TPI in EXTEM and INTEM tests and determination of the reference limits of the indicators TPI, CFT, MCF: 1) TPI - The index of thrombodynamic potential is an indicator that determines the ability to coagulate in both coagulation systems. Patients with liver cirrhosis have changes in clot formation that are not unidirectional - some of them have impaired coagulation with insufficiently formed clot, and in another - in a state of hypercoagulation. The differences in the results are in group I with bleeding, compared to those in group II, where the values are within the reference range; 2) MCF in the INTEM panel shows no significant difference between the two groups. Patients with cirrhosis of the liver form a clot with similar strength, despite the disturbed coagulation in both systems. 3) MCF in the EXTEM panel shows significantly lower values for group I, with bleeding, ie. there is a significant difference in MCF between the internal and external coagulation system.

9. FIBTEM parameters: FIBTEM is an additional panel to EXTEM and INTEM, which shows abnormalities in hemostasis in patients with liver cirrhosis. 1) CT - has less but significant significance in the fibrinolysis test. The use of this parameter alone to assess bleeding is insufficient, but in combination with other parameters, shows significant changes in fibrinolysis in patients of group I with liver cirrhosis and bleeding; 2) MCF does not show significant differences in the three groups compared to the other parameters of the panels, but has deviations from the norm in patients with varicose bleeding.

10. Parameters of HEPTM: 1) CT in both groups with liver cirrhosis shows a tendency to shorten the clotting time, especially in group I and changes suspected of having endogenous heparinization, also in group I; 2) MCF results differ for the first two groups compared to the control. Hemostasis changes were observed in patients with liver cirrhosis, the presence of endogenous heparinization, regardless of the presence of a bleeding episode, especially in patients of group I.

11. Comparative analysis of the results of ROTEM and conventional hemostasis tests: 1) INR shows a significant difference in the two groups with liver cirrhosis compared to the control group. There is no significant difference between the bleeding group and the non-bleeding group; 2) aPTT - there is no difference in values between the first 2 groups and dependence on the presence of bleeding. In the control group, the values of aPTT are within the reference range.

12. Diagnostic reliability of conventional hemostasis tests:

It is established that

1) low diagnostic value and lack of dependence between the parameters of EXTEM and INR, as a parameter of the external system of hemostasis is present. There is no connection between the ROTEM and INR indicators; 2) There is no connection between the indicators of INTEM and aPTT, as a parameter of the external system of hemostasis; 3) Increased platelet count and increased CFT values in INTEM are present; 4) Decreased platelet count and increased CFT (prolonged clot formation time) values in INTEM are present; 5) The prolonged time for CFT does not depend only on the platelet count, which in both groups is in a close range.

Conclusions and contributions

Based on the obtained results, Kamen Danov MD forms 5 inferences, which are related to the aim and tasks of the dissertation topic and the results of the individual scientific details of the study.

The contributions of the dissertation, according to the author are 6. For the first time in our country 1) a study was conducted on the applicability of the method of rotational thromboelastometry to assess hemostasis changes in patients with liver cirrhosis and esophageal varices; 2) hemostasis changes in patients with bleeding from esophageal varices were studied by rotational thromboelastometry; 3) a comparative analysis of the conventional tests for

hemostasis in patients with cirrhosis with bleeding and without bleeding was performed and the results were compared with the parameters of rotational thromboelastometry; 4) the threshold values of the thrombodynamic potential of patients with hepatic cirrhosis with bleeding and without bleeding have been established; 5) the data from the comparative study are systematized and the diagnostic reliability of the conventional tests for examination of the hemostasis and the parameters of the rotational thromboelastometry is determined; 6) the diagnostic criteria for rapid assessment of the risk of bleeding in patients with liver cirrhosis using rotational thromboelastometry are systematized.

In connection with the dissertation a total of 4 articles have been published in Bulgarian journals.

In conclusion, the dissertation of Kamen Danov MD is very well planned, executed and written in the correct Bulgarian language and scientific style, in sufficient volume and convincingly illustrated with tables and figures. The developed topic is contemporary, relevant in theoretical and practical aspects. The use of modern rotational thrombelastometry as a diagnostic method for assessing hemostasis, for assessing the risk of bleeding and the need for blood transfusions, for assessing the therapeutic strategy in hemostasis disorders, high reliability and speed of examination are extremely important for the activities of UMHATEM "N. I. Pirogov". In this regard, Kamen Danov MD is a "pioneer" in the introduction of rotational thrombelastometry for the overall assessment of hemostasis in patients with liver pathology and bleeding. The theoretical conclusions from this study are original and important for Bulgarian gastroenterology.

In terms of its content, inferences and scientific and practical contributions, the presented dissertation fully meets the requirements of the Law for the development of the academic staff in the Republic of Bulgaria and the Regulations for the development of the academic staff in the University Hospital "N. I. Pirogov" EAD - Sofia and I strongly recommend to the members of the respected scientific jury to award Kamen Valentinov Danov MD the educational and scientific degree "Doctor" in the scientific specialty "Internal Medicine".

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Sofia

Prof. Fani Martinova, MD, PhD, DSc