Reviw Article

COAGULOPATHIES OF LIVER DISEASES: A NARRATIVE REVIEW

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ABSTRACT

Background: Liver is considered to be one of the synthetic organs regarding coagulation factors. Patients with liver disease undergo a rebalanced state, where a procoagulant state is also established along with an anticoagulant state. The risk of thrombosis is as common as the risk of bleeding.

Aims and objectives: The following discussion will highlight the importance of rebalanced system and will explain the role of common coagulation tests in patient with advanced liver disease. This discussion will also emphasize the limitation of common coagulation tests and will describe an approach to such patients in clinical settings.

Material and Methods: A narrative literature review utilizing PubMed and OVID as databases was carried out in August 2018. Keywords used were: "Advanced liver disease", "Coagulation disorders", "Thrombosis and embolism" and "Coagulopathy of liver diseases". This literature search was confined only to studies performed on human beings and published in English language only.

Keywords: Coagulation disorders, Liver diseases, Thrombosis.

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INTRODUCTION

Liver as a synthetic machinery is responsible for the synthesis of many clotting factors, hormones and other substances. Amongst the clotting factors are procoagulants and anticoagulants. These include Vitamin K dependent clotting factors (II, VII, IX and X), protein C, protein S and Anti-thrombin-III, Thrombomodulin, Fibrinogen, and many others. Normally, there is a balance between procoagulant and anticoagulants in blood with mild shift towards anticoagulant state so that the blood is prevented from de novo thrombosis[1]. Bleeding is commonly seen in cirrhotic patients in the form of variceal bleeding, ecchymosis and easy bruisibility. The clinicians are inclined to prevent these bleeding episodes by giving Fresh Frozen Plasma (FFP), Tranexamic acid and even whole blood as a preventive strategy in decompensated liver cirrhosis[2]. Similarly, Prothrombin time (PT), Activated Partial Thromboplastin time (aPTT) and Platelets count are considered to be markers of bleeding risk in these patients and preventive measures are taken in patients who need surgical intervention even if there is no active bleeding in such cases[3].

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Clinicians in their daily clinical practice encounter so many liver patients having decompensated liver disease and portal vein thrombosis simultaneously, making their job difficult whether to initiate or vice versa anticoagulation therapy to such patients.

The following discussion will answer the following questions:

1 Is Decompensated liver disease solely an anticoagulant state?

2 Do PT, aPTT and Platelets count reflect the true risk of bleeding in such patients?

3 Is the risk of Thrombosis increased in Decompensated liver disease?

4 How Thrombotic states are managed in Decompensated Liver Cirrhosis?

SEARCH STRATEGY AND RESULTS

To answer these questions, literature search was conducted using PubMed (MESH) and OVID as search database engines. The following bolean terms were

used in PubMed and OVID searching:

1 Coagulation disorders AND Advanced Liver disease

2 Coagulation OR bleeding disorders of liver diseases

3 Thrombosis and Embolism AND Advanced liver disease

4 Coagulopathy of liver diseases NOT of other systemic diseases

In addition, search term of "Coagulopathy of liver diseases" was also utilized in Google scholar to extract additional relevant articles. A limit of "2012 till date" was applied. All these original papers/reviews/essays/guidelines were extracted and saved for review processing. Duplications were then subtracted and preliminary library of 30 results was made. The references of all these selected 30 articles were then individually searched by each author to find out high yield relevance accordingly.

The significant articles published between 2012 to August 2018 were selected for this review. The high yield variables and information were extracted from these articles. The "QualSyst" checklist was utilized

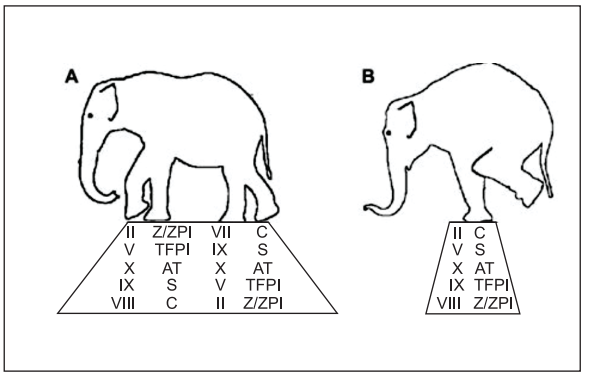

Fig1: Hemostatic balance (Courtesy Mareaune Hoffman)16.

A. Under normal conditions, there is excess of procoagulants and anticoagulants considered necessary for minimum hemostatic functions. This functional excess maintains hemostatic stability even during stress.

B. The levels of procoagulants and anticoagulants are reduced in liver diseases. The balance between these proteins may be maintained but this hemostatic balance is critically at risk during stresses and infections.

Table 1: Limitations of main laboratory tests in liver diseases

Lab tests	Limitations
Platelet counts	- No defined Cutoff value for bleeding in liver diseases
	- Does not reflect true platelet function in liver diseases
	- Lab Machine counted platelets are not true depiction of actual platelet counts in liver disorders
International Normalized Ratio (INR) and Prothrombin Time (PT)	- Both INR and PT measure procoagulants only
	- These tests are not validated for chronic liver diseases
	- The inter-labs variations and high cost of reagents are other limitations
	- Not a true predictor of bleeding in patients with liver disorders
Activated partial Prothrombin Time (aPTT)	- Reflects procoagulant system defects only
	- Requires expertise levels and costly standard reagent for proper measurement
	- Severity of liver disease is difficult to determine with aPTT only due to multiple confounders like raised factor- viii levels in chronic liver diseases
Bleeding Time (BT) and Clotting time (CT)	- A time tested approach to determine platelet function in vivo
	- Being cumbersome, partly reflecting platelet count, so many confounders and having unclear value to determine bleeding tendency in CLD patients are main limitations
Procoagulant factor levels	- Availability is main issue
	- Significant lab variations
	- There is no proven link to bleeding in patients with CLD
Thrombin generation test	- Availability and expertise to interpret results are main limitations
	- Variables are not standardized
	- It is not validated to predict bleeding risk in CLD Patients
Platelet aggregation test	- Available only in specialized hematology labs
	- This test is not calibrated for thrombocytopenia
	- Poorly correlated with bleeding risk in CLD patients
	- Needs quick evaluation and interpretation after blood sampling from patient

for bias assessment risk. This list is basically used as a standard operational tool in systemic reviews.

All the important articles of last six years including Randomized controlled trials and systematic reviews/ meta-analysis were included in this review. Articles written in English language were included. Finally, a total of 14 articles, 7 belonging to PubMed, 5 from OVID and 2 from Google scholar were included.

DISCUSSION

After vessel / tissue injury, the first mechanism that tries to control bleeding is vasospasm when vascular collagen is exposed. This is followed by activation of Platelets and clumping occurs, resulting in platelets plug formation. In the meantime, the Coagulation cascade starts (by extrinsic and intrinsic pathways) and results in a clot formation. This clot is then lysed by Fibrinolytic system[4]. Tests for functionality of these mechanisms include, Platelets count, PT, APTT, Fibrin Degradation Products (FDPs) including D-Dimers and Fibrinogen Levels. Specialized tests include, Thrombin time, Euglobulin lysis time and Von Willi brand factor levels, Factor VIIIa levels, Protein C and S and Platelets aggregation studies[5].

Thrombocytopenia, considered to be a prognostic marker, is the result of many factors. These include platelets sequestration in an enlarged spleen, decreased Platelets production due to low synthesis and release of thrombomodulin from liver and Platelets functional abnormalities[6]. Other coagulation defects include, low Coagulation factors synthesis, low levels of Protein C and S, and Hypo / Dysfibrinogenemia. Similarly, increased production of Von Willibrand levels results in abnormal Platelets aggregation. It has been observed that the circulating levels of factor VIII are also increased[7].

From the above discussion, it is evident that both procoagulant and anticoagulants are reduced in quantity. It means that there is a re-balancing of hemostasis in the blood of patients with liver diseases (Figure1). Contrary to the thinking that there is an increased risk of bleeding in cirrhosis, there is increased risk of thrombosis also[8]. This is evident in the form of increased risk of Portal vein thrombosis (PVT) in these patients. Portal vein thrombosis is partly due to vascular stasis when the blood flows towards the fibrosed liver, but an additional factor in rebalanced hemostasis resulting in a procoagulant state. This results from secondary deficiency of Protein C and S, increased Von Willibrand factors and many other proposed abnormalities[9].

While investigating coagulation defects in liver diseases, it is important to note that routine tests like PT and a PTT do not reflect the true picture of coagulation defects. In most of these patients, despite prolonged PT and a PTT, the risk of bleeding is minimal. Similarly, prophylaxis for bleeding in these patients is not required as these patients can undergo surgical procedures in the presence of these coagulation abnormalities[10]. Similarly, these patients can undergo surgical procedures including liver transplant even if platelets count in between 50,000 to 70,000 / cmm. These patients do not require therapy before or during surgery for prophylaxis of bleeding, rather the use of Fresh Frozen Plasma in these situations may increase the risk of variceal bleeding by increasing the plasma volume and ultimately portal pressure[11]. It has been estimated that 100 ml of fluids or Fresh Frozen Plasma increases portal pressure by 1.03 mm of Hg. Thus 2000 ml of these fluids may increase the portal pressure by more than 20 mm of Hg; thus increasing the risk of variceal bleeding[12]. Therefore, band ligation is recommended for such patients before subjecting them to major surgery as they require intravenous fluids and blood products during surgery. In routine practice, while managing such patient for other conditions, a transfusion and fluid restriction policy is advised to prevent the development of volume overload and thus reducing the risk of variceal bleeding.

The management of Venous thromboembolism (VTE) including Portal Vein Thrombosis in these patients requires that these patients should be anticoagulated in similar manner as patients without liver diseases[13]. The problem is that PT, a PTT and INR are not good predictors of bleeding in such patients. Similarly, PT is prolonged before the start of anticoagulation (Table 1). For that purpose, Low molecular weight Heparins are much safer and can be used without dose reduction in these patients. Factor-X inhibitors (Rivaroxaban) is an option, but the dose should be reduced as elimination of these drugs is reduced if the GFR is less than 30 ml/ minutes and in patients with Child class B and C liver disease[14]. Data from larger cohorts of patients with portal vein thrombosis need to be collected to assess efficacy and safety of novel oral anticoagulants in these difficult-to-treat patients[15,16]. The main limitation of this manuscript is narrative nature. A large meta-analytic review is the need of the hour to critically analyze these shortcomings.

CONCLUSION

The misconceptions that patients with decompensated liver diseases are auto anticoagulated, along with the use of PT and aPTT as markers of risk of bleeding should be reconsidered. Research has proven that the risk of thrombosis is as increased as the risk of bleeding.

Shifting to other novel bleeding assessment parameters and applying a transfusion restriction policy in managing these patients is the need of the day. Fresh Frozen Plasma should be avoided in these patients when it is used for correction of coagulation defects and prevention of bleeding. Portal vein thrombosis should be treated to prevent the development of massive ascites, precipitation of hepatic encephalopathy and intestinal ischemia.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Ahmad F: Main ideas literature review.

Haider I: Literature review, manuscript write.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.