Blood Disorders in Patients with Obstructive Jaundice: A Literature Review

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Abstract

BACKGROUND: Mechanical jaundice is a pathological syndrome consisting in a violation of the outflow of hepatic bile through the bile ducts into the duodenum due to mechanical obstacles. The most common causes of mechanical jaundice are gallstone disease, malignant tumors, as well as cicatrictial stricture of the bile duct or the large duodenal papilla of the duodenum. All this leads to the development of renal-hepatic insufficiency. Thrombohemorrhagic changes develop in the vascular bed, leading to the development of disseminated intravascular coagulation syndrome. Prevention and treatment of cholemic bleeding in case of mechanical jaundice remains one of the complex problems of hepatobiliary surgery. This article is an overview of the causes and pathophysiological changes affecting hemostasis in mechanical jaundice, as well as the main points of treatment of hemostasis disorders in patients with mechanical jaundice.

AIM: This study aims to study the literature on homeostasis in patients with mechanical jaundice.

SEARCH STRATEGY: To conduct a systematic search for scientific information and to achieve this goal, an analysis of scientific publications in evidence-based medicine databases (PubMed), using specialized search engines (Google Scholar) and in electronic scientific libraries (CyberLeninka, e-library) was carried out from 2005 to 2020.

EXCLUSION CRITERIA: Summaries of reports, reports in the form of abstracts, and advertising articles.

RESULTS: The mechanisms that affect hemostasis in obstructive jaundice can be considered from four perspectives: The first relates to Vitamin K deficiency in obstructive jaundice, the second describes the effect of ongoing fibrosis and cirrhosis of the liver on hemostasis, the third analyzes the relationship between infectious-septic mechanisms and the hemostasis system, their clinical significance in patients with obstructive jaundice, and the latter involves the analysis of specific factors that manifest obstructive jaundice and may themselves affect the blood coagulation system.

CONCLUSION: Understanding the pathophysiology of hemostatic changes in patients with cholestasis and, more generally, liver disease is a clear way to accurate diagnosis and treatment. The combination of good knowledge with careful examination of each patient can lead to the most promising result.

Introduction

The liver is the most important organ providing metabolic support and suprasystemic functions of organic synthesis in the body [1]. The functioning of its tissues determines the formation of most of the blood proteins, the restoration of anaerobically oxidized substances, and the synthesis of many non-protein components. These processes are maintained due to the high complexity and metabolic activity of the organ, which makes it vulnerable to damage associated with changes in the external and internal environment [2]. An additional negative factor may be the susceptibility of the auxiliary systems of the liver associated with the gastrointestinal tract, a high probability of diseases, especially in the elder people [3], [4]. The proportion of the latter in the population is constantly increasing.

These problems make liver diseases and related pathological changes in the body, as a whole, very relevant. One of the important aspects can be the influence of hepatic pathology on the hemostasis system, since most of the important factors of its plasma coagulation link are formed in this organ.

Causes of Impaired Formation of the Blood Coagulation System in Liver Damage

As components of the protein-synthesizing function of the liver, many blood coagulation factors (fibrinogen, prothrombin, V, VII, VIII, IX, X, XI, XII, XIII,
Vitamin K Deficiency in Obstructive Jaundice

Vitamin K is a fat-soluble vitamin that requires bile salts for absorption from the intestines. The bacterial flora of the intestine is also involved in the metabolism of bile salts or produces a small amount of Vitamin K. Thus, with the development of intra- or extra-hepatic cholestasis, there is a decrease in the absorption of Vitamin K in the intestine, which leads to Vitamin K deficiency in patients with obstructive jaundice. These patients often present with hemorrhagic diathesis despite having an almost normal coagulation profile as measured by prothrombin time [15], [16].

In addition to prothrombin time, measurement of PIVKA levels (and especially PIVKA-II, or des-gamma-carboxylated prothrombin) is used to assess the degree of Vitamin K deficiency, but this research has a high risk of erroneous results if hepatocellular carcinoma has not been excluded. Parenteral administration of 10 mg of Vitamin K replenishes serum levels, normalizes prothrombin time, and prevents bleeding episodes.

It is well known that malignancies that cause obstructive jaundice, and especially pancreatic adenocarcinoma, can affect coagulation through various mechanisms. In addition, it has been shown that acute pancreatitis (which can be caused by choledocholithiasis) is accompanied by a pre-thrombotic state, mainly due to stimulation of the vascular-platelet link [13].

Thus, the mechanisms that affect hemostasis in obstructive jaundice can be considered from four perspectives: The first relates to Vitamin K deficiency in obstructive jaundice, the second describes the effect of ongoing fibrosis and cirrhosis of the liver on hemostasis, the third analyzes the relationship between infectious-septic mechanisms and the hemostasis system, their clinical significance in patients with obstructive jaundice, and the last one involves the analysis of specific factors that manifest obstructive jaundice and may themselves affect the blood coagulation system.

Disturbances in the production of blood clotting factors by damaged hepatocytes are combined with a decrease in the absorption of Vitamin K due to a lack of bile in the intestine. Vitamin K is an important cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of a variety of specific peptide-linked glutamic acid residues in inactive hepatic factor II, VII, IX, and X precursors. The resulting gamma-carboxyglutamic acid residues convert precursor substances into active hemostasis factors, which are subsequently secreted into the blood by liver cells.

Despite oral (together with bile acids) or parenteral administration of Vitamin K in a patient with jaundice, difficulties in correcting hemostasis disorders in these patients may remain [8]. Bleeding episodes or thrombotic manifestations may aggravate the clinical condition of a patient with jaundice. These manifestations require a careful clinical and laboratory approach to make an accurate diagnosis and ensure effective treatment [9].

Bacterial invasion plays a key role in the pathophysiology of hemostasis disorders in patients with obstructive jaundice. Numerous studies revealed that obstructive jaundice significantly contributes to increased bacterial proliferation in animal models as well as in humans [10], [11]. In these cases, intestinal bacteria and endotoxins can penetrate the mucosa and reach the mesenteric lymph nodes or other distant tissues, causing a systemic inflammatory response. As a consequence, septic complications and multiple organ failure develop in a significant proportion of these patients. Triggering the coagulation cascade, primarily through tissue factor (TF) activation, is a key parameter for the final outcome; excessive and unbalanced production of TF and subsequent uncontrolled activation of the external complex of the blood coagulation system can even lead to clinically manifest thrombotic events and/or disseminated intravascular coagulation (DIC).

Systemic inflammation is also a component of the pathogenesis in two chronic liver diseases accompanied by cholestasis: Primary biliary cirrhosis and primary sclerosing cholangitis, in which a hypercoagulable state has been registered [12]. In addition to septic or inflammatory complications that lead to hypercoagulability, the underlying pathology is crucial for identifying additional pathophysiological pathways for hemostasis impairment in obstructive jaundice.
Progressive Liver Failure and Cirrhosis

With the development of liver fibrosis and the progression of liver failure in conditions of cirrhosis, the presence of general disorders in the hemostasis system becomes available for laboratory research and then gets clinical manifestation. Continued evolution toward cirrhosis in a patient with malignant cholestasis is rare, since in most cases, survival time determines the progression of the tumor process. However, in benign diseases leading to obstructive jaundice, such as primary sclerosing cholangitis, cirrhosis of the liver is an inevitable result. The possibility of liver cirrhosis should be evaluated in every patient with a history of chronic cholestatic syndrome of unknown etiology.

Thrombocytopenia in liver cirrhosis is significant and is mainly due to increased platelet retention in the enlarged spleen (congestive splenomegaly) [17]. In addition, it has been suggested that these changes are facilitated by a decrease in thrombopoietin levels, since liver transplantation increases thrombopoietin production and reverses thrombocytopenia depending on the size of the spleen [18].

However, conflicting results have been published regarding plasma thrombopoietin levels in chronic and acute liver failure [19], [20], [21]. Other possible causes of thrombocytopenia have been proposed, such as reduced platelet half-life, the presence of autoantibodies, especially in patients with primary biliary cirrhosis or sclerosing cholangitis, folic acid deficiency, and ethanol toxicity for elements of megakaryocytopoiesis, especially in alcohol abusers [22], [23], [24], [25]. Finally, the presence of DIC, even subclinical, is still controversial [26].

Platelet dysfunction is common in patients with chronic or acute liver disease. Platelet aggregation in vitro in response to stimuli such as ADP, arachidonic acid, collagen, and thrombin has been shown to be impaired [27], [28]. It has also been shown that the interaction of platelets with the vessel wall under normal blood flow conditions is disrupted [29]. Changes in aggregation can be caused by disturbances in the mechanisms of signal transmission within the vascular-platelet link of hemostasis, an acquired deficiency of the accumulation pool, and a decrease in the level of arachidonic acid (necessary for the synthesis of thromboxane A2) in the platelet membrane [30], [31].

In addition, increased production of prostacyclin and nitric monoxide (which are potent inhibitors of platelet function) by endothelial cells may contribute to impaired platelet function in vivo [32], [33]. Finally, the interaction of platelets with the vascular wall may be impaired in patients with liver disease due to proteolysis of platelet receptors by plasmin or due to reduced hematocrit [34], [35].

In addition to platelet defects, in patients with impaired liver function, there is a decrease in the synthesis of blood coagulation factors. Almost all proteins involved in the coagulation cascade are synthesized in the liver, and for the most of them, the liver is the only place of production. The degree of decrease in the activity of procoagulant factors depends on the degree of liver damage, the presence of hemorrhagic diathesis, how disease proceeds, and its prognosis.

Standard coagulation tests do not show the presence of abnormalities until plasma levels of the relevant factors fall below 30–40% of the norm, and specific tests for each factor, although available, are not so informative and are relatively rarely used in routine clinical practice.

Since factors V and especially VII have a short half-life (12 and 4–6 h, respectively), their determination can provide informative results in acute liver failure. Since factor VII and fibrinogen are acute-phase proteins, their content increases at the initial stages of the process, and a significant decrease may indicate the development of DIC [36].

The main qualitative disorder that may accompany liver failure is dysfibrinogenemia, which is characterized by abnormal polymerization of fibrin monomers as a result of increased activation of fibrinogen molecules.

Diffuse liver diseases are also characterized by the presence of hyperfibrinolysis, which is manifested by a reduction in the time of euglobulin clot lysis and increased levels of D-dimers, FDP, and fibrin and is mainly due to reduced clearance of fibrinolytic agents, mainly tPA. In addition, low levels of α2-antiplasmin and a thrombin-activated inhibitor of fibrinolysis (due to impaired protein production by hepatocytes) may contribute to the progression of this process [37]. It is not yet clear whether hyperfibrinolysis is entirely a primary procedure or partly the result of continuous activation of coagulation [38], [39].

An exhaustive analysis of the primary and secondary hemostatic mechanism in 32 patients with liver cirrhosis showed that all indicators, except for the content of fibrinogen, factor XIII, plasminogen inhibitor, and TFPI, were impaired. PFA-100 after ADP stimulation, PT activity, factor X, factor V, fibrin, and plasminogen independently correlated with the severity of cirrhosis and had deviations from the normal mean in the early stages of the disease, suggesting that impaired hemostasis is present even in subclinical liver cirrhosis [40].

Despite that hemorrhagic diathesis is the end result of changes in the hemostatic system in patients with cirrhosis, these patients often present with portal vein thrombosis. Thus, in the event of a sudden deterioration in the condition of a patient with cirrhosis, a careful determination of the presence of portal vein
thrombosis should be carried out [41]. However, the development of thrombosis may be associated with the state of local blood circulation and, mainly, with a decrease in the volume of blood flow in the portal vein. This aspect is confirmed by the results of a research suggesting that clinically significant coagulopathy in cirrhosis is a myth rather than a reality, since these patients have adequate thrombin levels when determining endogenous thrombin activity [42], [43].

**Systemic Inflammation/Sepsis and Impaired Hemostasis in Patients with Obstructive Jaundice**

The occurrence of DIC in obstructive jaundice and its association with biliary tract infection was discovered quite a long time ago [44]. Elevated plasma levels of endotoxins, cytokines, and C-reactive protein in patients with obstructive jaundice and the presence of bile infection were transiently normalized after bile duct drainage [45].

Infectious agents enhance the production of some cytokines: Interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF), which are able to activate hemostasis and, subsequently, fibrinolysis by stimulating the external pathway of blood coagulation [46]. Endotoxins produced by bacteria stimulate the expression of TF on macrophages and the activation of blood coagulation through oxidative processes [47].

A relationship has been demonstrated between TF levels and markers of lipid peroxidation activation, increased coagulation potential, and fibrinolysis in patients with cirrhosis. Hyperactivation of fibrinolysis delays the activation of coagulation due to consumption of the coagulation factor and inhibition of fibrin polymerization, and also reduces platelet adhesion and aggregation [48]. Platelet function is further impaired by increased prostacyclin levels, which are induced by endotoxins and endothelin through nitric oxide formation [49].

How these sepsis-related events become bleeding remains controversial and requires further study.

The relationship between coagulation and inflammation is still not well understood. Activation of hemostasis processes, in addition to fibrin synthesis and platelet aggregation, leads to a change in the functional state of the cells of the vascular wall, which contributes to an increase in the activity of leukocytes [50]. On the other hand, sepsis and septic shock are known to induce activation of the extrinsic coagulation pathway, which has been clinically demonstrated by ELISA measurements of TF in septic patients [51].

TF overexpression is usually blocked by a TF pathway inhibitor (TFPI) [52]. However, patients with sepsis who have an insufficient TFPI balance mechanism have a poor prognosis because the excess TF production cannot be compensated [53].

Other anticoagulants such as antithrombin and activated protein C have been found to have anti-inflammatory properties [54].

An important pathway that explains the relationship between sepsis and coagulation processes is the stimulation of F3 expression in peripheral blood and endothelial cells, which usually do not have this mechanism, directly by lipopolysaccharides and peptidoglycans or indirectly by TNF-α, VEGF, IL-1β, IFN-1γ, and many other inflammatory mediators [55].

F3 is the gene encoding TF. TF is a protein having a large extracellular domain (219 residues), a small transmembrane domain, and a small cytoplasmic component. Its role is to form a trimolecular complex with FVIIa and FX (activation of FX) and, thus, to initiate coagulation [56].

Normally, F3 is expressed mainly in the brain, lungs, placenta, and kidneys, and after stimulation, in peripheral blood and endothelial cells. Its traces are found in plasma [57].

F3 is also expressed with another splice variant that includes exons 1, 2, 3, 4, and 6 of F3 and results in the production of alternatively spliced human TF (as-HTF). As-HTF is a protein that lacks the transmembrane and cytoplasmic components of TF and has a unique termination sequence due to exon 4/6 fusion. Both TF and as-HTF have the same active catalytic domain and the same procoagulant properties, acting as propagators of the coagulation process at the boundaries of newly synthesized thrombi. TF is associated with the membrane, while ac-HTF circulates freely [58].

The role of TF in the systemic inflammatory response accompanying cholestasis has been explored in several researches [59], [60]. These researchers studied the procoagulant activity of peripheral blood monocytes in patients with obstructive jaundice and in the control group without jaundice. Mononuclear cells from patients with jaundice, tested immediately after isolation, showed low levels of procoagulant activity, which, however, were significantly higher than in cells from control (p < 0.01). In addition, after short-term incubation in cultures with and without endotoxin, these cells presented greater procoagulant activity than controls (p < 0.001). No significant differences were found in procoagulant activity between patients with and without malignancy in both groups. A decrease in the degree of obstruction of the biliary tract led to a decrease in the level of bilirubin in the serum and the procoagulant activity of monocytes. Endotoxin-induced procoagulant activity of monocytes was approximately 3 times higher in deceased patients with jaundice than in survivors (p < 0.001).
In rabbits with induction of jaundice by ligation and separation of the bile ducts (15 days), endotoxin-induced procoagulant activity of monocytes was markedly increased compared to operated animals without induction of jaundice (p < 0.005). In all cases, procoagulant activity was determined by analyzing the activity of TF. An increase in TF production by mononuclear phagocytes may explain the activation of the hemostasis system in severe jaundice.

A well-known model of how systemic inflammation, other than generalized sepsis, can be associated with coagulation in clinical practice is chronic liver disease with cholestasis syndrome caused by primary biliary cirrhosis or primary sclerosing cholangitis. These conditions are characterized by better outcomes of bleeding from varicose veins and less blood loss during liver transplantation, which indicates the presence of hypercoagulability. In their presence, the levels of factors VIII and vWF increase, while the levels of proteins C, S, Z, antithrombin III, macroglobulin a2, and heparin cofactor II decrease. This imbalance, along with the presence of antiphospholipid, anticardiolipin, and antineutrophil cytosolic autoantibodies, contributes to hypercoagulability in many patients [49], [61].

Hypercoagulability in patients with primary biliary cirrhosis and primary sclerosing cholangitis was explained by elevated fibrinogen and platelet hyperactivity, which is not observed in liver diseases that are not accompanied by cholestasis (chronic hepatitis C and alcoholic cirrhosis). It is believed that these changes are the result of pronounced systemic inflammatory activity. Whether this phenomenon involves platelets directly or indirectly (through TF expression) has not yet been elucidated [53].

### Treatment of Hemostasis Disorders in Patients with Obstructive Jaundice

Vitamin K deficiency is likely in patients with cholestatic conditions. A dose of 10 mg Vitamin K for 3 days may compensate for the prolongation of prothrombin time in these patients. Intravenous administration of Vitamin K is fraught with anaphylaxis. Subcutaneous administration is characterized by an inconsistent rate of absorption, intramuscular injections should be avoided due to the risk of hematoma [62].

It is considered that thrombocytopenia does not pose a threat if the number of platelets exceeds 50,000 in 1 µl. If the platelet count slightly exceeds this limit during bleeding or before a surgical procedure, a platelet transfusion is recommended. One unit of platelet concentrate increases the number of circulating platelets by about 10,000 in 1 µl. The increase in platelet count is limited in patients with hypersplenism, since most of the transfused platelets are retained in the enlarged spleen. The use of recombinant thrombopoietin to correct the platelet count in patients with liver cirrhosis has different reviews in the literature [63].

Prolonged bleeding time, mainly associated with low platelet counts, can be compensated for by administration of 0.3 µg/kg 1-deamino-8-D-arginine vasopressin (DDVAP), especially if surgery is required. Although DDVAP increases plasma levels of factor VIII and vWF, its exact mechanism of action remains unknown [64].

Coagulation factor deficiency can also be corrected with fresh frozen plasma [65]. The introduction of the latter at a dose of 10–20 ml/kg of body weight can reduce the prothrombin time to <3 seconds. However, the duration of the correction of coagulopathy lasts no more than 12–24 h (since the half-life of FVII is 4–6 h). Failure to correct after adequate transfusion of fresh frozen plasma indicates the presence of dysfibrinogenemia or FDP. Fluid overload is a common complication when large amounts of fresh frozen plasma (1–1.5 L) are administered. In addition, the risk of infection should not be underestimated. Solvent-detergent treatment of plasma reduces this possibility, but it is found to be deficient in factor VIII, proteins S and C, and α2-antiplasmin.

Plasmapheresis has been used instead of fresh frozen plasma infusion with similar results in treating coagulopathy without the risk of volume overload [66].

An alternative solution is infusion of prothrombin concentrates containing only Vitamin K-dependent coagulation factors, which can only partially compensate for coagulopathy and leads to the risk of thromboembolic complications and DIC.

Cryoprecipitate contains factors VIII and XIII, fibrinogen, vWF, and fibronectin. One unit of cryoprecipitate (20–30 ml) is enough for every 10 kg of body weight. Administration to cryoprecipitate is indicated when plasma fibrinogen levels fall below 100 mg/dl as a consequence of DIC or massive blood transfusion.

A new approach is the introduction of recombinant activated factor VII (rFVIIa). In preliminary reports, a dose of 80 µMg/kg normalized prothrombin time over 12h in patients with cirrhosis. However, the prolongation of prothrombin time caused by rFVIIa does not necessarily reflect the hemostatic efficacy and treatment that should be taken in patients with subclinical DIC [64].

In hyperfibrinolysis and concomitant bleeding, there is a need for antifibrinolytic agents, such as ε-aminocaproic acid, tranexamic acid, or aprotinin. Again, thromboembolic events are a serious threat; thus, the use of these agents should be discontinued after successful management of hemostasis. With aprotinin, the relative risk of these complications may be lower [67].
Conclusion

Impaired hemostasis in a patient with obstructive jaundice is multifactorial and difficult to assess. The general rule is that a doctor should treat a patient, not the results of laboratory tests. Information obtained from coagulation tests should be carefully studied and interpreted in clinical practice. Uncomplicated but prolonged benign cholestasis will lead to hemorrhagic diathesis. In these cases, prophylactic administration of Vitamin K should be carried out. If septic complications and/or pancreatic involvement are superimposed, the net effect on hemostasis may be a prothrombotic state; thus, low-molecular-weight heparin may be useful in some patients. Unresolved cholestasis can gradually lead to liver dysfunction and cirrhosis. In these cases, there are more generalized hemostatic disorders affecting almost all pathways: Thrombocytopenia, decreased synthesis and clearance of coagulation factors and inhibitors, dysfibrinogenemia, hyperfibrinolysis, and excessively DIC, along with portal vein stasis and thrombosis, may converge in one patient. In the treatment of such a patient, the recommendations of the hematologist regarding the administration of platelets, fresh frozen plasma, cryoprecipitate, prothrombin complex precipitates, recombinant factor VII, DDVAP, or antifibrinolytic agents are very important. When a malignant neoplasm is documented, the situation becomes more complicated. Adenocarcinomas of the mucosa (e.g., pancreas or colon) and hepatocellular carcinomas can cause activation of hemostasis. Thromboembolic complications, especially in the first case, are frequent and serious complications, leading to a poor prognosis. The use of low-molecular-weight heparin fractions in these patients, in addition to preventing thrombosis and embolism, may compromise tumor growth by inhibiting the mechanism of TF-mediated angiogenesis. Understanding the pathophysiology of hemostatic changes in patients with cholestasis and, more generally, liver disease is a clear way to accurate diagnosis and treatment. The combination of good knowledge with careful examination of each patient can lead to the most promising result.

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