

Hemostasiologic Changes during Hepatobiliary Surgery in Patients with Obstructive Jaundice: Pathophysiology and Clinical Considerations

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Citation

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Abstract

Aim: The aim of this article was to present an overview of the hemostaseologic changes in patients with obstructive jaundice undergoing bile duct and hepatic surgery, with respect to the risk assessment for developing postoperative liver insufficiency, intraoperative and postoperative hemorrhage or thromboembolism. **Source:** Relevant articles from the MEDLINE databases (1976-2010) were extracted and reviewed, using the following key words: "obstructive jaundice", "liver resections", "hemostasis", "perioperative hemostaseologic changes", "perioperative bleeding", "liver insufficiency", and "perioperative thromboembolism". **Main findings:** The development of intra- and postoperative hemorrhages and the occurrence of thromboembolic incidents in patients with obstructive jaundice are due to changes in coagulation and fibrinolysis. They depend on the etiopathogenesis of the main disease and inflammatory changes in the biliary system, as well as on the duration of mechanical obstruction and the scope of surgical intervention. The occurrence of perioperative hemostatic complications does not always correlate with the extent of abnormalities in the analyzed perioperative laboratory hemostaseologic parameters. **Conclusion:** Further research of the association between perioperative hemostaseologic changes in patients with obstructive jaundice of malignant and benign origin would contribute to the risk assessment of possible intra- and postoperative hemostatic complications and liver insufficiency, as well as to the prophylaxis of these complications.

INTRODUCTION

Obstructive jaundice is a syndrome, representing malignant or benign mechanical dysfunction of the extrahepatic biliary system. The most common causes of extrahepatic cholestasis are choledocholithiasis, tumors of the bile ducts and pancreas, postoperative structures, primary sclerosing cholangitis, acute or chronic pancreatitis, etc. The formation of mechanical obstruction with intrahepatic cholestasis is mainly associated with carcinomas of the intrahepatic ducts, primary sclerosing hepatitis, bacterial cholangitis, hepatic metastases, etc.

PATHOPHYSIOLOGIC BACKGROUND

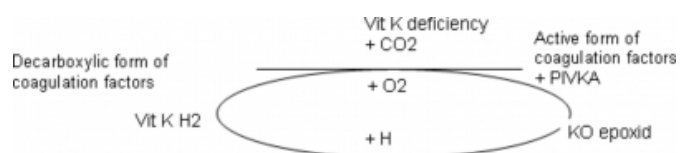
The development of hemostaseologic changes in obstructive jaundice is mainly a sequel of vitamin K-deficiency and related synthesis of coagulation factors and protease inhibitors.

VITAMIN K-DEFICIENCY

The fat-soluble vitamin K is a cofactor in the synthesis of factors II, VII, IX and X, as well as of anticoagulant proteins II , S and Z [1, 2]. During its decreased resorption in case of obstructive jaundice, the non-carboxylic vitamin-K-dependent factors of coagulation serve as biologically inactive precursors (PIVKA-protein induced in vitamin K absence) [2] (fig.1.).

Figure 1

Fig. 1. Vitamin K and its impact on coagulation



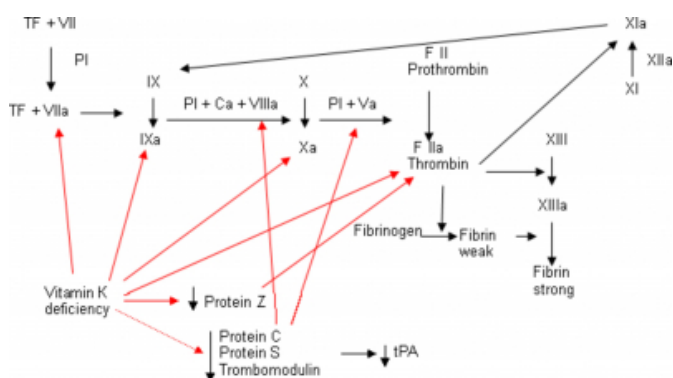
The prolongation of prothrombin time (PT) corresponds to severe vitamin K -deficiency. A PT longer than 16.5 seconds is associated with moderate to severe vitamin K -deficiency and factor activity less than 30%, while a PT shorter than 16.5 seconds is indicative for factor deficiency lower than 40%

[3]. According to many authors, however, there is no definite correlation between the severity of factor deficiency and the degree of changes in the PT and partial thromboplastin time activated

(APTT) [4, 5], and, therefore, the informativeness of the PT and APTT values, as far as the intraoperative transfusion needs are concerned, is not very high [3,5, 6,7]. Pathologic values of PT and APTT do not always correspond to the concentrations of critical factors. Usually, there is a sufficient physiologic reserve [5]. The main reason is that the relation between the measured coagulation times and the factor concentration is not linear. Since the tests evaluate a combination of factors, if more factors have mild to moderate diminution, the PT and APTT will paradoxically decrease to a greater degree, than in case of one factor's reduction of up to 50% [5]. Currently available global screening tests cover a reference value range assessing a decrease in coagulation factors' activity no lower than 30-40% [2, 8].

Figure 2

Fig. 2. Role of vitamin K-deficiency in the coagulation system



K-vitamin dependant factors affect primarily the activity of Factor (F) VII and secondarily, the anticoagulation protein Z (short plasma half-life). Protein Z is the factor localizing the thrombin. Due to this protein, thrombin binds to the phospholipid surface of the endothelial cells. In case of protein Z-deficiency, the thrombin is washed away to the peripheral microcirculation, thus creating the possibility for microthrombosis. There is a positive correlation between protein Z-deficiency and intraoperative bleeding [9].

Theoretically, it can be suggested that during a short period within the initial stage of obstructive jaundice, there is a balance between the reduced procoagulant and anticoagulant activities (fig. 2.). This suggestion is based on the following observations:

1. Concomitant decreases of F VII and protein C, due to their equal plasma half-life times.
2. Reduced thrombin generation. As a biologic mediator, thrombin has multiple functions: it is the major regulator of the procoagulant, anticoagulant and fibrinolytic activities and vascular endothelial functions.

Reduction of fibrinolytic activity, since protein C is an activator of (tissue plasminogen activator)

3. tPA.

The administration of vitamin K aims at compensating the deficiency of active factors belonging to the external coagulation system.

All three types of hemostaseologic changes, i.e. hypocoagulability, hypercoagulability and hyperfibrinolysis, are observed in clinical practice. The risk of developing hemorrhage or thrombosis is individually determined. The variants of hemostaseologic changes and the probability of hemostaseologic complications depend mainly on some additional pathophysiologic features, namely:

1. Duration of the obstructive jaundice;
2. Etiology of the biliary obstruction – benign or malignant;
3. Hemostasiologic changes associated with the surgical intervention;
4. Development of SIRS or sepsis in the course of obstructive jaundice;
5. Accompanying liver diseases.

DURATION OF OBSTRUCTIVE JAUNDICE

In case of mechanical obstruction, there is an increased biliary permeability, due to regurgitation of the bile coming from the caniculae paracellularly to the blood, with diminution of the bile production. Bile acids accumulate in the hepatic tissue and induce hepatocyte apoptosis by activating the protein kinase C and magnesium-dependent endonucleases. Clinically, this results in the development of progressive hepatic insufficiency [10]. The hepatic dysfunction begins on the 5th day from the obstruction onset. Its degree correlates with the hepatic level of bile acids [11]. Therefore, the hemostaseologic changes will relate not only to vitamin K-deficiency, but also to the occurred hepatic dysfunction.

ETIOLOGY OF BILIARY OBSTRUCTION AND HEMOSTASEOLOGIC CHANGES

MALIGNANT ETIOLOGY OF OBSTRUCTION JAUNDICE AND HEMOSTASEOLOGIC CHANGES

In case of malignant process, the thromboembolic complications are more frequent, than these of excessive bleeding. During obstruction, thrombosis is observed in 40 % of the patients, although clinical expression of thrombosis has never been presented in these patients [12]. The activation of blood coagulation is a reaction of the organism caused by/and in response to the tumor and is manifested by vascular irritation, change of blood viscosity and excessive release of tissue factor

(TF). The patient immobilization contributes to this process as well [13].

The most common malignant processes associated with the obstructive jaundice are:

PANCREATIC CARCINOMA

The increased circulating carcinoma mucin CA19-9 interacts with the thrombocytic α -selectin and leucocytic L-selectin. It seems that this interaction generates abundance of microthrombi in the thrombocytes, without any production of thrombin [2].

In situ, in the presence of reduced tissue factor pathway inhibitor (TFPI) and plasminogen activator, formations of TF, prothrombin and fibrinogen can be found in the tumor. TF participates also in the angiogenic control, namely, in the up-regulation directed towards increased vascular endothelial growth factor (VEGF) production and in the down-regulation directed towards decreased thrombospondin production. The expression of TF is a bad prognostic mark [2]. It is the principal pathophysiologic step in the beginning of DIC in all malignant tumor patients [12]. There is also an augmentation of TF in 77% of the poorly differentiated pancreatic adenocarcinomas and in 20% of the well-differentiated ones [14].

LIVER CARCINOMA

1. Cholangiocarcinoma is a malignant infiltration of the bile ducts, which leads, in most cases, to a postoperative liver insufficiency without typical deviation in the preoperative hemostaseologic and functional laboratory tests.

2. Hepatocellular carcinoma with characteristic

hemostasiologic abnormalities of dysfibrinogenemia, high level of decarboxylated prothrombin, apoptic hepatocellular carcinoma cells HepG2, responsible for the development of intrasinusoidal microthromboses [2].

BILE DUCT CARCINOMA

In case of Klatskin's tumor, a liver resection should also be carried out. From all perioperative complications, severe (acute) postoperative liver insufficiency is the principal cause for mortality, followed by intraoperative and postoperative haemorrhage and sepsis, with rates of complications of 38%, 29% and 21% respectively [15]. Preoperatively, these patients have normal hemostaseologic indexes with insignificantly increased fibrinogen degradation products (FDP). Intraoperatively, during the mobilisation of the liver, an activation of the fibrinolysis begins. With termination of the operation, the fibrinolysis activation diminishes and normalises, except in patients with cirrhosis [16].

Cholestasis owing to an obstructive biliary malignancy is associated with postoperative complications related to a proinflammatory state, an impaired hepatic synthesis function, and a potential derangement of hemostasis. Obstructive cholestasis is associated with a procoagulant state, despite an impaired vitamin K-dependent coagulation factor synthesis [17].

BENIGN ETIOLOGY OF OBSTRUCTIVE JAUNDICE AND HEMOSTASEOLOGIC CHANGES

In the remote 1982, I. I. Filimonov and V. I. Shestakov carried out an exhaustive study of the dynamics of hemostatic dysfunctions among patients with benign obstructive jaundice [18]. Concerning the choledocholithiasis, they observed significant pre- and postoperative hypercoagulability with increased platelet aggregation and inhibition of the fibrinolysis up to the 5th – 7th postoperative day. In the presence of superposing inflammatory factors, such as cholecystitis and cholangitis, they observed preoperative and postoperative hypercoagulability with a peak on the 5th and 7th day, and significant inhibition of the fibrinolysis (about 48-57% of the preoperative level) with a peak on the same 5th – 7th day. Postoperative hemorrhagic complications occurred in patients of both groups [18].

OBSTRUCTIVE JAUNDICE AND SEPTIC

COMPLICATIONS

Enteral bacterial translocation and infection may lead to increased plasma levels of endotoxins, interleukins (IL-1, IL-6) and tumor necrosis factor (TNF) and D-Dimer [2, 19, 20, 21]. Endotoxins activate the monocytes and macrophages, which release the pro-inflammatory cytokines TNF, IL-1, IL-6 and IL-8. This activates the external route of coagulation, the complement and kinin systems [2, 22]. In patients with obstruction of the biliary pathways, the monocyte procoagulant activity has been proven to be three times higher than normal [2]. The released cytokines and endotoxin induce the TF expression in monocytes and the adhesion of thrombocytes via the P-selectin and thrombospondin [2, 22, 23]. On its part, the TF/VIIa complex stimulates the cytokine production, thus completing the formation of a vicious circle [23]. The TF balancing mechanism is the TFPI. TFPI binds the endotoxin and inhibits the production of TNF and nitric oxide (NO) [22]. In case of persisting cholestasis, the liver parenchyma is extremely vulnerable and there is a risk of generalized postoperative sepsis as a sequel of the chronic overloading of the hepatic reticuloendothelial system [24]. Most commonly, the combination of hepatocytic dysfunction and endotoxemia results in multiple microthrombosis and triggering of the coagulation cascade with resultant disseminated intravascular coagulation (DIC) [25].

HEMOSTASEOLOGIC CHANGES IN OPERATIVE TRAUMAS

Tissue injuries resulting from an operative trauma lead to the release of various mediators and activation of coagulation. At the site of primary thrombus formation, increased vascular permeability occurs, accompanied by the invasion of granulocytes, monocytes and macrophages in the injured tissue. Stimulated endothelial cells produce adhesive molecules, selectins, which realize the adhesion of neutrophils. The leukocytes activate and release various mediators, such as platelet aggregating factor (PAF), cathepsin G, leukocytic proteins, and cytokines, such as TNF, IL-1, IL-6 and IL-8, which participate in the regulation of coagulation and fibrinolysis.

SECONDARY CHRONIC HEPATIC DISEASES, SUCH AS HEPATITIS AND LIVER CIRRHOSIS, ACCOMPANYING THE OBSTRUCTIVE JAUNDICE MAY ADDITIONALLY CONTRIBUTE TO THE VARIETY OF HEMOSTASEOLOGIC

DEFECTS.

According to the degree of hepatic dysfunction, hemostaseologic changes can be subdivided into three groups [26]:

1. Hemostaseologic changes of mild degree presented by a small reduction in factor VII; in this case, an insignificant prolongation of the PT is observed [27].
2. Hemostaseologic changes of moderate degree presented by deficiency or shortened half-life time of the vitamin K-dependent factors. On the basis of the acute phase reaction, the levels of F VIII and vWF are increased. In rare cases, there is diminution of the fibrinogen. The aPTT can be prolonged because of the F IX reduction and/or the F VIII:C increase [28].
3. Hemostaseologic changes of severe degree presented by deficiency of all factors and inhibitors, thrombocytopenia and thrombopathy, dysfunction factors, dysfibrinogenemia and activated fibrinolysis.

An unsteady hemostatic equilibrium, lacking thromboembolism or hemorrhage, is most frequently established between the prothrombotic and hemorrhagic factors with low, yet balanced levels [3]. The dysfunction of this delicate balance, caused by different factors (operations, infections, etc.), may lead to either of the two severe complications, bleeding or thrombosis [1, 29, 30]. A. Tiede (2007) has suggested the predominant role of procoagulant factors' deficiency, in comparison to this of proinhibitors, while J. Thachil (2008) has observed states of hypercoagulability in a case of hepatic lesion as well [3, 24]. The laboratory analyses prove a state of "pseudo-DIC", while during the obductions, only some proofs for fibrin deposition exist and the clinical cases of DIC are very rare [30]. This abnormal profile, comprising increased intravascular coagulation and fibrinolytic phenomenon (the so-called accelerated intravascular coagulation and fibrinolysis phenomenon (AICF)), manifests increased levels of fibrinopeptide, prothrombin fragments F1+2 and D-dimers. AICF correlates closely with the high level of endotoxin in the portal blood [30]. In fibrinolysis, it can develop a "steady-state" status of the pro- and anticoagulant factors. In case of cirrhosis, hyperfibrinolysis is associated directly with the Child-Pugh scale and with the presence of ascites. The ascitic fluid presents increased fibrinolytic activity, which correlates directly with the level of endotoxin [30]. In general, the tendency for a change in the hemostatic

balance is close to the fibrinolytic state, which is not seen in all patients, because some of them generate adequate quantities of thrombin [2]. According to P. Innerhofer (2006), the thrombin generation can be normal, despite the presented pathologically low values of normal blood coagulation tests [5].

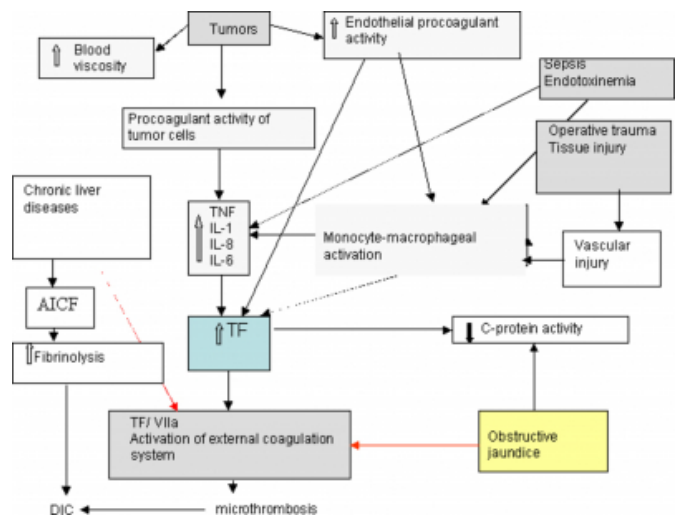
However, the combination of a low platelet number, reduced platelet function, increased levels of NO and prostacyclin, associated with low levels of the coagulation factors II, V, VII, IX and X, may still result in intensive bleeding after a minimal trauma.

Biliary surgery in patients with cirrhosis is associated with increased mortality and morbidity. The rate of complications following choledochotomy approximates 30%, distributed equally between mortality (50%) and morbidity (50%) rates. In this case, prolonged κ and albumin values below 35g/l are associated with 29% mortality and 38% morbidity and 33% mortality and 40% morbidity, respectively [31].

Influence of the anesthetics. A common opinion is that all modern employed anesthetics (exception for Halothane), are appropriate for anesthesia in the biliary surgery. The general anesthesia leads to reduction of the hepatic blood flow, because of systemic vasodilatation and some negative inotropic effects. According to P. Zalunardo, 2003, it would be good if the used medicines are not dependant on hepatic blood flow, enzymatic activity, and protein binding [32]. Concerning the influence of anesthetics on the blood coagulation potential, researches and analyses are made principally on experimental animals. Isoflurane, Halothane, Sevoflurane, as monoanesthesia or in combination with Xenon, lead to augmentation of prothrombin time and reducing of the fibrinogen concentration [33]. Sevoflurane suppresses the platelets aggregation by inhibition of the thromboxane κ 2 synthesis [33,34]. In opposite to propofol and sevoflurane, isoflurane does not influence the bleeding time [35]. The effects of anesthetics on the blood coagulation are mainly due to additional factors having indirect effect such as concomitant diseases influencing the hemostasis, use of medicaments having direct influence on the blood coagulation system, and the effect on the catecholamines associated with the operation and the emotional stress.

Figure 3

Fig. 3. Common pathophysiologic route of hemostaseologic changes in sepsis, tumors, and operative trauma.



CONCLUSION

In obstructive jaundice, the activation of external coagulation system is incomplete. The hemostaseologic changes are determined by additional pathophysiologic situations (fig. 3.). The risk for developing hemorrhage or thrombosis is individual for each patient and depends on various factors.

The development of intra- and postoperative hemorrhages and tromboembolic incidents in patients with obstructive jaundice are due to abnormalities in coagulation and fibrinolysis, depending on the etiopathogenesis of the main disease and inflammatory changes of the biliary system, as well as on the duration of mechanical obstruction and the scope of surgical intervention. Further research of the relation between perioperative hemostaseologic changes in patients with obstructive jaundice of malignant and benign origin would contribute to the risk assessment of possible intra- and postoperative hemorrhagic complications and tromboembolic incidents, as well as to the prophylaxis of such complications.

The occurrence of perioperative hemostatic complications does not always correlate with the extent of perioperative abnormalities in laboratory hemostatic parameters. A hemostaseologic assessment of the risk for developing such complications should be performed for each patient.

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