

Review paper

The risk of complications of endoscopic procedures in patients with liver cirrhosis

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Abstract

Endoscopy methods involve diagnostics as well as therapy. Endoscopic techniques have a small but definite incidence of complication, so endoscopy should not be performed routinely but only on the basis of indication. The typical endoscopic procedures used in diagnostics and therapy of liver cirrhosis are endoscopy of upper and lower gastrointestinal tract. Other techniques are less common. Significance of endoscopy procedures increases in case of chronic progressive liver diseases, independently of etiology, where changes in gastrointestinal tract are observed in 87% of patients.

Key words: liver cirrhosis, esophagogastroduodenoscopy, colonoscopy, portal hypertension.

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Introduction

Cirrhosis of the liver and its complications

Cirrhosis of the liver should be considered as chronic, diffuse liver disease characterized by abnormal liver cyto/angioarchitecture, vascular shortcuts, and pseudonodular lesions. The presence of liver fibrosis alone, irrespective of its severity, cannot be treated as cirrhosis. Cirrhosis criteria are differentiated; we categorize cirrhosis on the basis of: etiological, morphological, and functional criteria (compensated/decompensated), disease biochemical activity (active/inactive), and clinical criteria such as portal, postnecrotic, dysmetabolic, biliary, and splenomegal [1-3].

Etiological factors

The most important causes of chronic liver disease and consequent cirrhosis include hepatotropic viral hepatitis (HBV, HDV, and HCV), alcohol, toxins, certain drugs and chemicals, autoimmunological diseases, metabolic disorders such as fat metabolism disorders (currently the leading cause of liver transplantation

indications in the United States), storage of iron, copper, α -1-antitrypsin deficiency (other causes are rare), bile ducts diseases, hepatic veins disease, and portal veins confluence vessels diseases.

Clinical picture

The clinical picture of liver cirrhosis is intense and varied, and this, along with the ultimate survival, is determined by the variety of complications (either selective or collective) in almost all systems. In some patients, there are no significant clinical ailments and symptoms, and cirrhosis is diagnosed accidentally, e.g. during abdominal surgery. In most patients, cirrhosis is progressive, even after elimination of the causative agent, e.g. effective treatment of HCV infection or suppression of HBV replication. The consequences of rebuilding the cirrhotic liver, independently of the initial causative agent, include portal hypertension with all associated effects, persistent or intermittent neuropsychiatric disorders, portal encephalopathy, increased susceptibility to infection, and progressive impairment of numerous hepatic metabolic functions,

including metabolic disorders of medications and hemostatic functions. The liver is the organ of synthesis of numerous coagulation factors, anticoagulants, fibrinolytic proteins, thrombopoietin (the hormone that stimulates the production of platelets). The liver also affects the course of coagulation and fibrinolysis by removing excess clotting factors or fibrinolysis, as well as the products produced during these processes. The final effect and range of hemostatic hepatic dysfunction in cirrhosis is very different: from the absence of any clinical manifestations of these disorders, through massive bleeding, to the thrombosis, especially of the portal vein confluence vessels, which is often the first manifestation of HCC involving the cirrhosis of the liver [2-8].

Endoscopic examination in patients with cirrhosis

Endoscopy is defined as all medical procedures related to the endoscopic examination of tubal and cavernous organs, with specialized tools equipped with a light source and a suitable imaging system. Endoscopic examination may have diagnostic and/or therapeutic nature. This should be performed only after written consent obtained from the patient or his/her legal representative, and only in case of strict indications, taking into account absolute or relative contraindications, often observed in patients with advanced liver disease. The procedure should be explained to the patient beforehand, as patient's knowledge in this area facilitates cooperation and increases the effectiveness

of endoscopic examination. In the absence of cooperation, and at the same time with the patient at risk threatening his/her life (e.g. hemorrhage from the gastrointestinal tract), we perform the procedure under general anesthesia, which unfortunately may aggravate and consolidate the symptoms of encephalopathy.

The proper organization of the work of the endoscopic laboratory, quality and maintenance of the equipment, appropriate skills and knowledge of the staff, and proper preparation of the patient for examination improves the safety of the procedure related to possible adverse effects primarily of physical (equipment), rarely chemical and biological factors present in treatment rooms, and it also reduces the risk of equipment damage. We also need to be aware that endoscopic procedures involve a small risk of the staff involved in the examination – the risk related to the same factors as these of the patient. It is a pragmatic element of the profession, and applies to the entire personnel performing the examination [4, 8].

The complex diagnostics and treatment of advanced liver diseases including liver cirrhosis may involve all known endoscopic techniques and procedures. In practice, the most frequently performed endoscopic tests in this group of patients are examinations of the upper gastrointestinal tract (esophago-, gastro-, duodeno-, entero-, fistulo-, cholangioscopy, balloon enteroscopy) of the lower gastrointestinal tract (recto-, sigmo- colonoscopy), and of biliary tract (cholangioscopy, endoscopic retrograde cholangiopancreatography), less frequently endoUSG, or laparoscopy [8-13]. This is due to the fact that changes in the gastrointestinal tract in patients with cirrhosis of the liver are observed in approximately 87% of patients. Actually, gastrointestinal changes in patients with cirrhosis can be divided into: 1) associated with portal hypertension; 2) as a consequence of portal hypertension (Table 1). These changes that are the consequences of portal hypertension within gastrointestinal tract and coagulation disorders, most often increase the risk of complications during endoscopic, especially surgical procedures.

Changes not associated with portal hypertension, which occur more frequently in patients with cirrhosis than in the average population, include: 1) esophageal damage following reflux esophagitis and esophageal thrush; 2) different gastric mucositis; 3) gastric and duodenal ulcers (they often have asymptomatic course 37-70%, recurrent with tendency to bleeding); 4) characteristics of bleeding diathesis visible on mucous membranes of tubular organs of gastrointestinal tract. In 82% of patients with liver cirrhosis, helicobacter pylori (HP) infection has been shown to be present irrespective of age [5, 10]. Such a high frequency of HP

Table 1. Complications and consequences of liver cirrhosis

Development of collateral circulation – esophageal varices and varices of other gastrointestinal tubular organs and their secondary consequences (hemorrhages, eating disorders, drug metabolism disorders)
Gastro-, entero-, portal colopathy and their consequences (mucosal bleeding)
GAVE – “melon skin”, “snake skin”, and the consequences of bleeding
Ascites and its consequences (e.g. spontaneous bacterial peritonitis, hernia, circulatory-respiratory failure)
Splenomegaly, usually with hypersplenism
Hepatic encephalopathy
Cholestasis
Hepatic-renal syndrome
Hepatopulmonary syndrome
Emaciation
Primary HCC-carcinoma (also HCC/ChCC)
Immune system disorders and increased risk of infection

infection undoubtedly affects the incidence of mucosal inflammation and gastric and duodenal ulcers in patients with cirrhosis. Therefore, endoscopy of the gastrointestinal tract in patients with cirrhosis of the liver is a basic tool in:

- diagnosis and differentiation of complaints and symptoms that may be associated with involvement of gastrointestinal tract tubular organs (e.g. dyspeptic symptoms, difficult or painful swallowing, gastrointestinal pathology, or suspicion of such pathology revealed by other methods, e.g. USG);
- diagnosis of causes and treatment of bleeding from gastrointestinal tract as the consequence of portal hypertension and hemostatic disorders in these patients,
- assessment of the effectiveness of pharmacological, endoscopic, and surgical treatment, and the consequences of portal hypertension and its causes [3-5, 8, 10].

Endoscopy of upper gastrointestinal tract

This examination is possible and safe only after consideration all significant contraindications including: lack of cooperation with the patient (which is a frequent case during encephalopathy), acute peritonitis, perforation symptoms of peptic ulcer, and less frequently observed in patients with cirrhosis: acute esophageal inflammation, asthma attack, acute respiratory failure, unstable coronary artery disease, aortic aneurysm, pregnancy, and cervical instability. It is estimated that the risk of serious complications during esophagogastroduodenoscopy does not exceed 1/500 per examination, and the risk of death is 1/10,000. It is obvious that this risk is higher in patients who undergo endoscopic procedures and, of course, even greater in comparison to the general population (if endoscopic procedures, especially surgical procedures, are performed in patients with cirrhosis). This risk increases if endoscopic surgery is performed in the urgency mode, especially in patients with encephalopathy, active gastrointestinal hemorrhage, bleeding diathesis, and in advanced age. The most frequent complications of endoscopic procedures performed in patients with cirrhosis include hemorrhage, perforation, and generalized infections [3, 6-8, 10, 11, 13].

Hemorrhage

Table 2 presents endoscopic procedures with high-risk of bleeding according to the European Society of Gastrointestinal Endoscopy [11]. Depending on the risk of bleeding, performance of some of the procedures with the existing severe collateral circulation, severe

Table 2. Endoscopic procedures with high-risk of bleeding by the European Society of Gastrointestinal Endoscopy [11]

Endoscopic mucosectomy/submucosal dissection
Ampullectomy/sphincterotomy/dilatation with a large balloon
Endoscopic ultrasound plus fine needle biopsy
Polypectomy
Endoscopic band ligation
Transcutaneous gastrostomy
Dilatation of stenosis of the upper or lower gastrointestinal tract
Implantation of the stent into the esophagus, small intestine, or large intestine

ascites, or bleeding diathesis is not always technically feasible. At the same time, it has been demonstrated that diagnostic endoscopic procedures in patients with cirrhosis bring no specific high-risk complications, regardless of the nature of these problems. However, in our own practice, we have repeatedly observed hemorrhage during endoscope movement along well filled and thin-walled esophageal varices with endoscopic features of bleeding, and from gastric and duodenal mucosa with advanced gastric or duodenopathy features. Fortunately, such bleeding during endoscopy is technically quite easy to stop. Risk factors for bleeding, which are also risk factors for bleeding during endoscopic procedures in patients with cirrhosis, can be divided into three groups:

1. Risk of vascular origin (Table 3). The risk of bleeding in the natural course of cirrhosis affects 20-50% of patients with portal hypertension. Mortality during the first hemorrhage is currently 15-20%, and has decreased significantly in the last 20 years. Unfortunately, the risk of recurrent bleeding affects 40% of patients within 6 weeks (mainly 1 week) from gastrointestinal hemorrhage. The more advanced cirrhosis of the liver, the higher the mortality (in Child-Pough-class A patients, about 0%, and in Child-Pough class C about 30%), or if the cirrhosis is accompanied by primary liver cancer, septicemia, portal vein thrombosis, or acute alcoholic hepatitis. If bleeding is accompanied by ascites, the risk of death, as classified by D'Amico, reaches 57% [1-4].

2. Risk related to disorders of platelet number and function (Table 4). Thrombocytopenia in this group of patients is mainly due to the sequestration of thrombocytes in the spleen. In addition, decreasing of the cirrhosis progression, thrombopoietin synthesis in the liver, and hormone stimulating platelet synthesis are observed. Adverse effects on platelet count are brought by co-morbidities: other infections, alcoholism in some cases, malnutrition typically seen in advanced

Table 3. Causes of bleeding in patients with cirrhosis – vascular causes [7]

Portal hypertension, i.e. increase in portal vein pressure > 12 mmHg (standard 5-6 mmHg) with a simultaneous increase in gradient (WHVP) between the portal vein pressure and the pressure in inferior vena cava > 2-6 mmHg – called portal hypertension (PH):
– Presence of collateral vessels: esophageal, gastric, rectal, abdominal wall varices, less frequent in other areas
– Gastropathy, enteropathy and portal colopathy
– Gastric antral vascular ectasia (GAVE)
– Hypersplenism
Cytokine dysfunction related to vascular wall tension
Vascular stasis in lower limbs:
– Lower limbs varices
– Vascular stasis of hydrostatic origin (hypoproteinemia, venous and lymphatic compression of the pelvis in ascites, impaired drainage of the lower limbs)

Table 4. Causes of bleeding in patients with cirrhosis-thrombocytopenia [2, 7]

Sequestration of platelets in the spleen
Reduced production of thrombopoietin
Co-morbidities (viral infections, alcoholism, malnutrition)
Myelosuppression (viral infections, alcoholism, folate deficiency, drugs)
In HCV-infected immunological thrombocytopenia
Disordered platelet function
Disordered production
Acquired storage disorder
Disorders of secretion
Changed NO concentration (and altered activity)
Changes in the concentration of arachidonic acid in the platelet wall (less TXA ₂)
Effect of circulating paraproteins

Table 5. Causes of bleeding in patients with cirrhosis-deficiency of coagulation factors and fibrinolysis [2, 3, 7]

Coexisting vitamin K deficiency (impaired supply, absorption)
Very short half-life of factor VII (about 4-6 h – is the first to disappear), factor V is the next one
Consumption of coagulation factors
Fibrinolysis disorders
Reduced production of: plasminogen, TAFI – thrombin activated fibrinolysis inhibitor, alpha 2 plasmin inhibitor
Increase of tPA (tissue plasminogen inhibitor) – released from vascular endothelium with reduced hepatic clearance
Consumptive coagulopathy – rarely observed AICF syndrome

cirrhosis, and thrombocytopenia in the HCV-infected. The platelet function as such is also impaired. It is thought that platelet function disorders are the result

of their abnormal production (due to the reasons mentioned above), impaired bone marrow release, changes in NO-concentration and activity (especially its eNO isoform produced from arginine in endothelial cells). Interestingly, the low number and/or functional abnormalities of platelets in patients with cirrhosis are poorly correlated with an increased risk of gastrointestinal bleeding, but they do correlate with bleeding risk in surgical, endoscopic or dental procedures [2, 3, 14].

3. Risk related to deficiency of coagulation factors and disorders of fibrinolysis. Except for the von Willebrand factor released by vascular endothelial cells, other coagulation factors are synthesized in the liver. Factor VIII, synthesized mainly by endothelial cells of sinusoids, can be synthesized in extrahepatic locations. Hence, in post-inflammatory cirrhosis, the major cause of plasmatic diathesis involves a deficiency of coagulation factors synthesized in the liver, increasing with the progression of liver disease, or repeated gastrointestinal bleedings (Table 5). Typically, the first signs of deficiency are those with a very short half-life, i.e. factor VII (about 4 to 6 hours), and factor V. In patients with malnutrition (which we usually observe in advanced cirrhosis) and in patients with cirrhosis complicated by cholestasis, we additionally observe vitamin K deficiency, which determines the synthesis of factors II, VII, IX, and X. In this group of patients, there is also a slight excessive consumption of coagulation factors; the consumption is rapidly increasing with the coexistence of additional infections such as spontaneous bacterial peritonitis or a shock [7, 11, 13, 15, 16].

The causes of bleeding diathesis in patients with cirrhosis associated with fibrinolysis are also complex. These include: reduced production of plasminogen, thrombin-activated fibrinolytic inhibitor (TAFI), and α -2 inhibitor of plasmin; the increase of tissue plasminogen inhibitor (tPA) released from vascular endothelium with decreased hepatic clearance, and rarely observed (apart from cancer or severe infections complicating cirrhosis of the liver) consumptive coagulopathy in the course of infection, which requires differentiation between hyperfibrinolysis (rarely observed in cirrhosis of the liver), disseminated intravascular coagulation (DIC), and AICF syndrome (Accelerated Intravascular Coagulation and Fibrinolysis) present in 30% of patients with cirrhosis [2, 7].

Therefore, it is obvious that the risk of most endoscopic procedures is increasing with the rise of portal hypertension and hemostasis disorders, and is statistically significantly higher in patients with Child C or MELD score > 11.5. In case of need for endoscopic surgery, especially in the group of patients with high-risk bleeding (polypectomy, ECPW, mucosectomy/

submucosal dissection), a standard procedure before surgery in patients with platelet count $< 50,000/\text{mm}^3$ should involve platelet transfusion or administration of nonprotein thrombopoietin receptor agonists (e.g. eltrombopag), especially in patients with cirrhosis associated with HCV infection. When prothrombin time exceeds 20 s, freshly frozen plasma should be administered. Alternative treatment involves a withdrawal from certain procedures, such as polypectomy, unless the patient is prepared for liver transplantation. Adenoma progression to gastric adenoma is generally slow and appears to be often longer than the patients' survival time, especially in active and advanced liver cirrhosis (Child C) [4, 7, 9, 11, 12, 14, 17, 18].

Perforation

Greater risk of perforation of gastrointestinal tract is associated with endoscopic examinations in patients with cirrhosis, in which the procedure is not only diagnostic but above all therapeutic in nature, e.g. any therapeutic treatment related to the inhibition and prophylaxis of esophageal or gastric varicose bleeding, particularly in patients with anomalies or other gastrointestinal pathologies (e.g. diverticula). Gastric mucosal bleeding, bleeding from angiodysplasia, or gastric vascular ectasia GAVE type are mostly difficult to inhibit, especially with frequently accompanying coagulation disorders. According to the recommendations of Consensus Baveno VI, withdrawal in many centers from sclerotherapy (EVS) and replacing it with o-rings or endoscopic bands (EVL) (this technique is preferred in our Department) in esophageal varices reduces the risk of perforation or "de novo" hemorrhage. However, in urgent cases (hemorrhage), initial sclerotherapy is often necessary (injection of sclerosing agent in the area of or into the lumen of varicose veins). This allows for better visualization of the esophagus or stomach mucosa, and continuation of the ligation of varicose veins. In case of gastric varices, administration of N-butyl-cyanoacrylate to the lumen of the varicose vein, optionally EVS/EVL combined, is still a preferred method. Nevertheless, the puncture and administration of the sclerosing agent to the wall of tubular organ of gastrointestinal tract, especially performed by an inexperienced endoscopist, often with an anxious patient, may lead to the administration of the agent outside the lumen of gastrointestinal tract [4, 8, 10, 18].

Infections

The problem of generalized infections resulting from endoscopic procedures is often underestimated.

However, it has been proven that cirrhosis of the liver is associated with disorders of many immune mechanisms – both humoral and cellular. In addition, in many people, cirrhosis coexists with other diseases associated with immunodeficiency, including AIDS patients, oncologic patients, post-organ transplants patients, or those during immunosuppressive or oncological treatment and radiotherapy. Endoscopic gastrointestinal treatment favors translocation of gastrointestinal bacteria to vessels or ascites, which is associated with a higher risk of developing sepsis or idiopathic peritonitis in these patients [3-5, 15, 16].

Endoscopy of the lower gastrointestinal tract

This examination is safe when we take into account the contraindications, which include: no cooperation with the patient, acute peritonitis, megacolon toxicum, unstable coronary heart disease, acute respiratory failure, and pregnancy. There are also relative contraindications when the examination is possible after careful medical evaluation of its potential benefits and risks. These include: blood coagulation disorders, large-sized hernia, acute inflammatory bowel disease, chronic circulatory failure, poor patient preparation, diverticulitis, a number of abdominal procedures performed in the abdominal cavity. Causes of complications and their nature in this group of patients are similar to those observed during endoscopic procedures in the upper gastrointestinal tract [1-3, 8, 10, 13].

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