CHOLELITHIASIS, CHOLECYSTECTOMY — WHAT COMES NEXT?

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Pathology of the biliary tract is an acute problem of the modern medicine. In recent decades, both in Russia and abroad, despite some advances therapy associated with the appearance on the market of new pharmacological tools for effective correction of functional disorders of the digestive system, there is a clear upward trend in the incidence of biliary system. And this trend is characterized by stability. Thus, according to scientific forecasting incidence of diseases of the digestive system in the next 15-20 years will increase in the world, at least by 30-50% due to the increase in the number of diseases which are based on stress, dyskinetic, metabolic mechanisms. These trends are also biliary system pathology. Cholelithiasis much "younger" and is found not only in the young, but also in early childhood. The disease began to appear quite often not only women but also men. Currently, the prevalence of biliary tract diseases range from 26.6 to 45.5 per 1,000 people.

Diseases of the gallbladder and biliary tract (dysfunction of the biliary tract to cholelithiasis) are among the most common and severe diseases of the digestive system. Their characteristic variety of clinical manifestations, duration of flow, prolonged aggravation cause frequent uptake of patients for medical help. The value of this pathology is determined not only medical but also social aspects, due to its frequent detection in most working-age population and high rates of temporary and permanent disability. Early diagnosis and treatment of diseases of the biliary system is of great clinical importance because of the impact of transformation opportunities of functional disorders of the biliary system in organic pathology — in chronic

cholecystitis and cholelithiasis, which occurs as a result of violations of the colloidal stability of bile and joining the inflammatory process. Interest in the problem is also due to frequent involvement in the pathological process of adjacent organs (liver, pancreas, stomach and duodenum) and the occurrence of severe complications leading to disability.

The most common form of gallbladder disease is cholelithiasis (gallstones). According to the results of statistical studies in recent years, cholelithiasis suffer almost every five women and one man 10. Approximately one quarter of the population over age 60 and 1/3 of the population older than 70 years have gallstones. There are many factors that contribute to stone formation. Mnemonic for remembering risk factors of cholesterol gallstones are 5F: Fat — fat (overweight), Forty — forty (age about 40 years or more), Female — woman, Fertile — childbearing age (estrogen, increased premenopausal leads to an increase cholesterol levels in bile and decrease motor-evacuation function of the gallbladder) and Fair — blond or blonde. Other risk factors include a high intake of fat and carbohydrates, a sedentary lifestyle, type 2 diabetes and dyslipidemia (increased triglycerides and low HDL). A diet high in fats and carbohydrates in the formation of obesity predisposes that leads to increased synthesis of cholesterol and bile hypersaturation. However, no direct correlation between excess fat intake and the risk of gallstone disease is not established, as studies on this subject have yielded conflicting results. Number of suspected "trigger mechanisms" are also numerous: an imbalance in the system enzyme HMG-CoA reductase and 7α-hydroxylase regulating the synthesis of cholesterol and its conversion into bile acids, reduction of cytochrome P-450 involved in the hydroxylation, the change in the content of lysolecithin , cholesterol, mucin, taurocholate, etc. Has not lost its relevance today and lithogenesis classical theory based on the complex: lipid metabolism, inflammation and cholestasis. Gallstone disease in most cases are asymptomatic. Gallbladder disease can clinically manifested symptoms: pain in the right hypochondrium or epigastrium radiating to the right shoulder and forcing the patient to lie down, and not relieved by defecation. Most often the pain is constant and not cramping in nature. A Danish study indicates

the prevalence of gallstones that "night pain in the right upper quadrant" is the clearest symptom in men, and the "strong and oppressive pain, provoked by fatty food" is a symptom that best correlates with the presence of gallstones in women.

Ultrasonography of abdomen is the method of choice for the detection of gallstones and has a sensitivity and specificity of 95% and ultrasound accurately identifies biliary sludge. CT, MRI and cholecystography are alternative methods of research in gallbladder disease. Endoscopic ultrasound detects even small gallstones (<3 mm) and may be required if the results of other studies cast doubt on the diagnosis. The laboratory results are generally normal unless complications developed. From 10 to 15% and calcified gallstones detected by X-ray survey of the right hypochondrium.

Clinical practice is applied the method of fraction chromatic duodenal intubation, which allows not only to characterize the bile itself, its lithogenicity, at a very early stage of the disease, but also to assess the functional capacity of the gallbladder and biliary tract. Endoscopic retrograde pancreatic-cholecystography is used for the diagnosis of choledocholithiasis or to exclude other causes of jaundice, as well as for the assessment of the pancreatic ducts.

Patients with asymptomatic cholelithiasis do not require treatment. The method of choice in the treatment of gallstone disease with clinical manifestations is currently cholecystectomy (CE). In modern biliarologia there is disagreement in the approaches to the treatment of subclinical and asymptomatic forms of cholelithiasis. In this situation, the doctor and the patient have a dilemma: on the one hand it is known that the earlier treatment undertaken, the better long-term outcome of CE. On the other hand there is high and the percentage of postoperative complications. Risk / benefit calculations are as follows: Suppose out of 10,000 patients with asymptomatic stones, 200 for 10 years will develop acute complications with a mortality rate of 2.5% (5 patients), 100 patients with acute pancreatitis will be 10% of deaths (10 patients). Thus, 15 patients die from complications of gallstones. If all 10,000 had CE, then die from surgical complications from 10 to 50 patients. While deaths from complications spread over 10 years. The risk of colic in patients with gallstones was not primarily

responsible for the clinical symptoms, decreases with age, and CE does not lead to a significant increase in life expectancy. In this regard, patients with "silent" stones do not need surgical treatment, and are subject to dynamic observation.

If, however, CE was performed in patients who had no clinical signs of gallstone disease, in some cases, subsequently they develop so-called postcholecystectomical syndrome (PCES). According to published data, 20-30% of patients develop PCES within a few weeks or months after CE. Etiopathogenesis of this syndrome in some cases obvious (the formation of stones in common bile duct, common bile duct strictures, choledocholithiasis, obstructive papillitis, pancreatic duct stenosis), but there are other options, which are not apparent in any anatomical abnormalities. This testifies to the functional pathology of biliary tract.

First PCES described in 1947, its features are the conservation of a number of symptoms that patients experienced before the operation or the occurrence of the first. These symptoms such as nausea, bloating, diarrhea, vomiting of bile, and the severity of abdominal pain, repeated and / or persist after CE. Such symptoms may occur in the early postoperative period of a few months or years. Although the term is used broadly PCES, but it includes both direct biliary tract pathology:

- Early PCES
  - *The presence of stones in the cystic duct stump and / or common bile duct*
  - *Bile duct injury / ligatures during surgery*
  - *Leaking bile*
- Late PCES
  - *The accumulation of stones in the common bile duct*
  - *Bile duct strictures*
  - *Stones and / or inflammation in the cystic duct*
  - *Papillary stenosis*
  - *Biliary dyskinesia*
  - *Extra bile causes which may also be associated with CE*
- Gastrointestinal causes
  - *Acute / chronic pancreatitis (and its complications)*

- *Tumors of the pancreas*
- *Hepatitis*
- *Diseases of the esophagus*
- *Ulcer*
- *Mesenteric ischemia*
- *Diverticulitis*
- *Organic or functional gastrointestinal disorders*
- *Syndrome of bacterial overgrowth in the small intestine (up to 57% after CE)*

➢ Extraintestinal reasons

- *Psychiatric and / or neurological disorders*
- *Coronary heart disease*
- *Intercostal neuritis*
- *Unexplained pain syndromes*

50% of these patients suffer from pancreatobiliary organic and / or gastro-intestinal disorders while other patients suffering from psychosomatic or not associated with the digestive system, diseases. In addition, 5% of patients after laparoscopic CE cause of chronic abdominal pain remains unknown. Probably because of nosological uncertainty prevalence PCES varies according to different authors from very low to 47%.

Stones of the common bile duct or cystic are the most common cause of PCES. They are classified as "left" or after "recurrent" in two or more years after surgery, respectively. They are identified using retrograde cholangio-pancreatography or by MRI, which has a sensitivity of 95-100% and specificity of 88-89% for the detection of stones in the bile ducts.

Numerous clinical manifestations of abdominal discomfort in patients PCES can be explained as follows. It is known that the gall bladder performs a number of functions (depositary, evacuation, concentration, suction, secretory, gate, hormonal and other) that provide synchronization of the sphincter apparatus of biliary pancreoduodenal zone. Loss of a functioning body and its physiological role takes

time for the body to adapt to the new conditions associated with the exception of gallbladder bile from the digestive processes and changes in exocrine function of the liver due to CE. Removed gall bladder leads to inevitable functional reorganization biliary system involving a complex set of relationships neuro-hormonal advancing due to loss of physiological function of gall bladder, and is an effective compensatory mechanism to slow down bile flow and its concentration in the ducts. In case of violation adaptive-compensatory possibilities hepatobiliarypancreoduodenal system due to the lack of gall bladder appear prerequisites for progression PCES. Some patients operated such adaptation does not occur at all, and develop diverse clinical manifestations PCES.

Gastroenterologist's practice more common shows variant of PCES, which flows by type of dysfunction or sphincter of Oddi dyskinesia (DSO) without anatomic stenosis. There are various classifications of the syndrome, including Rome III criteria, which are subdivided into 3 DSO biliary subtypes and one pancreatic. Typically, the second and the third part biliary subtypes, as well as in some cases the type of pancreatic DSO treated conservatively. Noteworthy Milwaukee classification for DSO, since it is defined and stages of research and methods of treatment, it is very convenient in practice, surgeons and gastroenterologists in practice (Table 1).

Table 1

Classification of sphincter of Oddi dysfunction by Milwaukee

Type	Clinical criteria	Prevalence of stenosis CO (%)	Treatment strategy
I	Typical biliary colic	65-86	Sphincterotomy
	Liver function tests increased twice		
	Common bile duct extended (diameter ≥ 12 mm) according to ERCP		
	The delay in the passage of the contrast agents according to the duodenum ERCP (> 45 min)		
II	Typical biliary colic	50	Sphincterotomy in patients with stenosis of the SB
	One or more (but not all) of the additional criterion		
III	Only typical biliary colic	28	Conservative treatment

We conducted a study of 54 patients diagnosed with postcholecystectomical syndrome aged 21 to 66 years period after CE from 2 to 17 years who underwent CE for asymptomatic cholelithiasis control group consisted of 35 people without the disease of the biliary tract. All patients performed clinical studies fractional minute sensing, biochemical bile, with the definition of indexes lithogenicity, dynamic ultrasound choledoch, according to testimony ERPHG. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association (as amended 2000 with the explanation given on the WMA General Assembly, Tokyo, 2004), the rules of Good Clinical Practice of the International Conference on Harmonization (ICH GCP), the ethical principles set out in the European Directive Union 2001/20/EC and the requirements of the national legislation of the Russian. The study protocol approved by the Ethics Committee of Kemerovo State Medical Academy and Rostov State Medical University, review and approval of research meet the requirements of national legislation. From each patient was obtained informative consent to participate in the study. Differences between the parameters of comparison were considered statistically different at $p \leq 0,05$.

The fractional duodenal intubation was found indirect evidence of duodenal hypertension in 14 patients (increase in volume and voltage portion of A) ($p \leq 0,05$), insufficiency of the sphincter of Oddi in 24 people, hypertonicity of sphincter of Oddi was detected in one person, the remaining function of sphincter of Oddi was retained. Only 7 patients with volume and tension portions C was within the normal range, the rest of these data were significantly higher ($p \leq 0,05$) control — 136,5±3,24 ml and 34,5±0,92 respectively, which indirectly indicating biliary insufficiency. Patients PCES group showed a statistically significant reduction of bile acids ($p \leq 0,05$) in all subjects, and the reduction of cholesterol and bilirubin ($p \leq 0,05$), lithogenicity codes were changed ($p \leq 0,05$) upward bile lithogenicity — cholate-cholesterol ratio (CCR) at PCES was 3,99±0,11 as in the control group 10,3±0,21. With dynamic ultrasound choledoch — choledochal diameter in all patients did not exceed 8 mm. Drugs against correction UDCA (Ursosan, Prospect Island PRO.MED.CS Prague, Czech Republic) 12 mg / kg body weight for 3 months and mebeverin (Duspatalin, Prospect

Island ABBOTT HEALTHCARE PRODUCTS, Netherlands) 200 mg 2 times a day for a month — 3 months and the amount of voltage portions C significantly decreased to 57,5±4,78 ($p \leq 0,05$), and CCR increased to 8,9±0,19, indicating a good reduction lithogenicity bile.

The mechanism of action of UDCA is multifactorial in patients with PCES is very important to her and choleretic and litholytic effects.

Choleretic effect. UDCA is hydrophilic, while many other bile acids are hydrophobic and therefore exert a cytotoxic effect on hepatocytes. These hydrophobic bile acids are toxic to the hepatobiliary system, causing apoptosis, necrosis and fibrosis. UDCA competes with the dominant endogenous bile acids when absorbed in the ileum due to its hydrophilicity. Stimulation of exocytosis in hepatocytes through activation of Ca-dependent protein kinase and leads to a decrease in the concentration of hydrophobic bile acids. Induction increases the excretion of bicarbonate cholepoiesis hydrophobic bile acids in the intestine.

Litholytic effect. UDCA is associated with decreased bile lithogenicity due to the formation of liquid crystal molecules of cholesterol, prevent the formation and dissolution of cholesterol. UDCA increases the proportion of bile acids in bile, reducing its glut of cholesterol and dissolves stones. UDCA did not affect the synthesis of cholesterol, but reduces its absorption in the intestine. UDCA promotes micellar solubilization due to the liquid crystalline phase. Noteworthy features of some clinical effects of UDCA. It turned out that it clearly reduces the appearance of "biliary dyspepsia", reduces the frequency and severity of attacks of biliary colic and eliminates dyspeptic symptoms, sometimes quite clearly shown in these patients with PCES.

Deciding on the appointment of myotropic therapy, we are faced with the need to use a drug that would selectively filmed abnormal spasm of SO, while not causing it atony. Such preparation was chosen miotropnym antispasmodic mebeverin hydrochloride. Merit-based drug mebeverin hydrochloride, which influenced his choice, were:

- sedative selectivity to the SO, significantly, by 20-40 times, higher than the effect of papaverine achieved by reducing the permeability of smooth muscle cells for Na^{+};
- normalizing, eukinetic, the impact on the smooth muscles of the intestine, helps eliminate functional duodenostasis, giperperistaltiki, spazmofilii, without the development of secondary hypotension, due to indirect reduction of outflow $K^{+;}$
- mebeverin metabolizes in the small intestine and enters the liver, and then the systemic circulation as already inactive metabolite without exerting any systemic effect.

Effect after administration of mebeverin occurs rapidly (within 20-30 minutes) and proceeds at around 12 hours, which makes possible its acceptance twice daily (prolonged form), while for older patients require dose adjustments. Mebeverin hydrochloride drug in these patients can be used for a long time, which is especially important for patients with DSO after CE.

Thus, the timely and proper evaluation of clinical symptoms developing in patients after CE, gives you the opportunity to choose the appropriate treatment and as a result improve the quality of life of patients with diseases of the hepatobiliary system.

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Article is dedicated to the gallstones, cholecystectomy upon asymptomatic gallstones. Pathogenetic mechanisms of postcholecystectomical syndrome in patients after cholecystectomy without evidence are described, as well as the methods of its diagnostics. Current data on the use of drugs with a high level of evidence and recommendations in the treatment of postcholecystectomical syndrome are represented. Article also provides our own research on the improvement of the motor-evacuating function of the biliary tract and lithogenicity of the bile after cholecystectomy in patients with gallstone disease.