Section A-Research paper

Differentiated tactics for the treatment of patients with acute cholangitis complicated by endogenous intoxication

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Annotation. *The study was based on 116 patients with mechanical jaundice of benign genesis, complicated by purulent cholangitis. In 35 patients with cholemic endotoxicosis after preliminary minimally invasive decompression of the biliary tract, various methods of treatment were used. In 11 patients (group I), traditional treatment including infusion and antibiotic therapy was used; in 12 patients (group II), plasmapheresis was used in combination with indirect electrochemical oxygenation (IECO) of plasma with sodium hypochlorite; and in 12 (group III) with additional plasma ozonation (PA with IECO + Ozone) and subsequent reinfusion of detoxified plasma. The developed differentiated stage-by-stage surgical tactics with the implementation of minimally invasive decompressions and the use of plasmapheresis allows to stop the phenomena of endotoxicosis, cholestasis and liver dysfunction and thereby improve the results of treatment of patients with acute cholangitis.*

Key words: *purulent cholangitis, endogenous intoxication, plasmapheresis, indirect electrochemical detoxification of plasma.*

Relevance. Purulent cholangitis is one of the most frequent and severe complications of benign and malignant diseases of the biliary tract. Acute purulent cholangitis and biliary sepsis are different manifestations of an infectious and inflammatory process that occurs locally and systemically [1,4]. Cholangitis and biliary sepsis are manifested by a complex of organic and functional, general and local pathological changes in the body as a result of the development of an infectious process in the bile ducts and occur when their patency is impaired and are observed in 17-83% of patients with choledocholithiasis, Fater's nipple stenosis, Mirizzi syndrome [2,6,10]. In patients with posttraumatic strictures of the bile ducts and cicatricial constrictions of biliodigestive anastomoses, cholangitis is detected in more than 80% of cases [1].

The inflammatory process in the biliary tract is characterized not only by a local purulent-destructive process, but also by systemic disorders that quickly lead to severe endogenous intoxication and pronounced organ dysfunction. This condition is most often considered as cholangitis, the severity of morphological and clinical manifestations of which is very diverse [3,7,10].

It is believed that without surgical intervention, acute purulent cholangitis leads to death in 100% of cases. Postoperative mortality, according to different authors, varies widely and amounts to 13-60% [3,6,8]. In the surgical treatment of cholangitis, significant progress has been achieved due to the introduction of modern minimally invasive interventions, but there are also a number of unresolved problems. One of them is cholemic endotoxicosis, accompanied by an increase in the level of metabolites in the blood plasma (bilirubin, urea, creatinine, residual nitrogen,

transaminases, oligopeptides of average molecular weight, etc.) [2,5,9,10]. Postoperative mortality varies widely and ranges from 8 to 27% [3,4,8]. Based on the fact that the main cause of mortality is endotoxemia, the question of detoxification therapy naturally arises. Plasmapheresis is the most studied method of adjuvant therapy. With convincing evidence of the effectiveness of plasmapheresis in purulent cholangitis, further studies are needed to increase its effectiveness by reducing the volume of plasma substitution and the possibility of reinfusion of purified plasma to patients.

Materials and methods. The study was conducted on the basis of the Samarkand branch of the Republican Scientific Center for Emergency Medical Care. The study was based on 116 patients with hyperbilirubinemia, acute cholangitis, biliary sepsis and severe biliary sepsis. The majority of patients were 74 women, 42 men. The average age of the patients was 61.3 ± 7.6 years.

Diagnostics of acute cholangitis and biliary sepsis are based on anamnesis data, clinical picture (Charcot triad, Reynolds pentad) and laboratory examination, which allow calculating the degree of organ failure on the SOFA scale (Sepsis organ failure assessment) and the severity of systemic inflammatory response according to SIRS criteria (Systemic inflammatory response syndrome). Clinical manifestations of acute cholangitis were chills, a sudden rise in body temperature to 38-40With a rapid decline. In 62% of patients, chills were accompanied by the appearance of jaundice on the first day of the disease. The most frequent clinical symptoms were pain, jaundice, fever. The classical Charcot triad and Reynold's pentad were relatively infrequent (in 36% and 11% of cases). Thus, there were no absolute reliable clinical signs to distinguish acute cholangitis from acute cholecystitis. Therefore, in the diagnosis of acute cholangitis, we preferred highly informative laboratory and instrumental research methods.

Laboratory and instrumental diagnostics, in addition to conventional clinical analyses, included the determination of the level of bilirubin and its fractions in blood serum, the activity of serum aminotransferases, alkaline phosphatase, protein content and its fractions, cholesterol, prothrombin, thymol and Sulema samples.

Noninvasive methods of preoperative diagnosis of acute cholangitis, biliary sepsis and pathology of the organs of the hepatopancreatoduodenal zone against which they occurred, in addition to physical examination, included ultrasound, computed tomography. Endoscopic examinations included choledochoscopy, fibrogastroduodenoscopy, laparoscopy, retrograde pancreatocholangiography. The final diagnosis was established during the operation by characteristic changes in the walls of the bile ducts and bile with the determination of microflora.

The most common cause of cholangitis and biliary sepsis was choledocholithiasis - 62.7%, acute destructive cholecystitis - 5.9%, breakthrough of echinococcal cysts in the choledochus - 5.9%, stricture of the terminal choledochus - 4.7%, stricture of the larger duodenal nipple - 4.3%, stricture of biliodigestive anastomosis and Mirizzi syndrome, respectively 4.1% and 4.3%.

All patients with acute cholangitis and biliary sepsis were subjected to surgical treatment. Depending on the type of operation, 6 groups of patients were identified, which are presented in Table 1.

Table 1

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Types of surgical treatment

№	*Operations*	*quantity*
1	Endoscopic papillosphincterotomy (EPST)	13
2	Percutaneous-transhepatic cholangiostomy (PTCS)	3
3	Cholecystectomy, choledocholithotomy, external drainage of the choledochus	68
4	Terminolateral hepatojunoanastomosis on a disabled loop of the Ru	14
5	Cholecystectomy drainage of the cystic duct by Abbe-Pikovsky	11
6	Choledochotomy, external drainage of the choledochus	7
	Total	**116**

The tactics of surgical treatment of patients with acute cholangitis complicated by biliary sepsis were strictly differentiated, while mainly using a three-stage method of decompression, plasmapheresis and sanitation of the biliary tract.

Decompression of the biliary tract allowed postponing radical surgery and performing it in a more favorable period. Choledocholithiasis with or without inflammatory stricture of the biliary tract, which caused the development of acute cholangitis, was considered indications for EPST and PTCS. In view of the initial severe condition at the first stage of treatment, the main task of the minimally invasive operation undertaken was considered to be the elimination of purulent cholangitis by decompression and restoration of the passage of bile into the duodenum.

According to the results obtained, all patients were divided into four groups: Group A - patients with mechanical jaundice without signs of an inflammatory reaction (SIRS = 0) - 41 patients; Group B - patients with mechanical jaundice and a slightly pronounced inflammatory reaction (SIRS one sign) (acute cholangitis) - 40 patients; Group C - patients with two or more signs of SIRS (biliary sepsis) - 28 patients; Group D - patients with two or more signs of SIRS and SOFA organ dysfunction > 0 (severe biliary sepsis) - 7 patients.

In 81 patients from A and B (41+40) groups, mainly (68 patients underwent cholecystectomy, choledocholithotomy and external drainage of the choledochus), one-stage surgical intervention was used.

Plasmapheresis (PA) was used in 35 patients from groups C and D (28+7), after preliminary minimally invasive decompression of the biliary tract. After the improvement of the patients' condition and normalization of peripheral blood parameters, surgical treatment was performed. Three subgroups were identified among these patients (Table 2).

Table 2

Characteristics of patients with biliary sepsis

Patient groups	*Traditional treatment*	*PA with IECO*	*PA with IECO and Ozone*	*Total*	*%*
Biliary sepsis	7	8	8	23	65,7
Severe biliary sepsis	4	4	4	12	34,3
Total	11	12	12	35	100

In 11 patients (group I), along with preliminary decompression of the biliary tract, traditional treatment including infusion and antibiotic therapy was used; in 12 patients (group II) plasmapheresis was used in combination with indirect electrochemical oxygenation (IECO) of plasma with sodium hypochlorite; and in 12 (group III) with additional plasma ozonation (IECO and Ozone) and subsequent reinfusion of detoxified plasma. Criteria for detoxification of exfused plasma, making its reinfusion possible, were determined according by N.M. Fedorovsky (2004) (Table 3).

Table 3

Criteria for detoxification of exfused plasma

Plasma parameters	Reinfusion criteria
PSMM level (according to Gabrielyan)	< 0.24 conv. un.
Hematocrit	< 27 Ed./ ML
Bilirubin total.	< 32 mmol / L
Creatinine	< 0.2 mmol / L
Urea	< 8 mmol / L
Total albumin concentration	> 35 g / l
Effective albumin concentration	> 30g / L
Binding capacity of albumin	> 0,86
Reserve binding capacity of albumin	> 10 g / l

In order to develop a rehabilitation program for patients with cholangitis and assess the feasibility of using extracorporeal detoxification methods, we set a goal to investigate the effect of plasmapheresis on the main biochemical and specific parameters of intoxication in patients with severe endotoxicosis with cholangitis.

Our proposed method of detoxification of the body in cholemic endotoxicosis (patent for invention UZ, No. IAP 04630), including the intake of exfused plasma, the addition of a solution of sodium hypochlorite with a concentration of 1200mg / l in a volume ratio of 10:1, holding the mixture at a temperature of 6-8oC, aspiration removal of sediment and reinfusion of autoplasm, characterized in that, that after adding a solution of sodium hypochlorite to the plasma , the resulting mixture is ozonated by bubbling with an ozone-oxygen gas mixture for 10 minutes, after that, the mixture is kept for 3-4 hours (without exposure to O3, the plasma exposure time is on average 8-12 hours (RU 2033190 C)).

Results and discussion. A comparative assessment of the dynamics of laboratory parameters during the treatment of patients of groups 2 and 3 revealed no significant differences. Hyperleukocytosis before surgical treatment is noted in both groups. However, after surgical treatment in group 1 patients, leukocytosis indicators normalize only by the time of discharge, which indicates a more pronounced purulent intoxication. At the same time, patients of groups 2 and 3 have a more rapid decrease and normalization of leukocytosis on the 5th postoperative day.

The initial increase in the leukocyte intoxication index (LII), a sharp increase on the day of surgery occurs in all the studied groups. In group 1 patients, there was a significant decrease in this

indicator by 46.9% by the time of discharge. On the contrary, patients of groups 2 and 3 showed a significant decrease in this indicator on day 6 (64.1%) and complete normalization by the time of discharge, which is associated with more effective relief of endotoxicosis.

Significant hyperbilirubinemia was noted in all patients. The highest rates of total and direct bilirubin followed by a slow decrease were found in group 1. On the contrary, in patients of groups 2 and 3, a decrease in total bilirubin was found by 79.7% in the first and by 85.4% on the 3rd day after surgery, which led to a faster normalization of this indicator. The slow decrease in bilirubin levels in group 1, despite decompression of the bile ducts, reflects the preservation of cholestasis and impaired liver cell function. Preliminary decompression and plasmapheresis in patients of groups 2 and 3 provided rapid relief (on day 3) of cholestasis, endotoxicosis, liver dysfunction.

Group 1 patients had high creatininemia numbers on the 1st day after surgery, which persisted for a long time in the future, which indicated hepatic-renal insufficiency in patients with severe endotoxicosis and cholestasis, which was aggravated by surgical trauma. On the contrary, in patients of groups 2 and 3, creatininemia remained within the normal range throughout the postoperative period, since preliminary decompression and plasmapheresis contributed to the prevention of hepatic-renal insufficiency. The effectiveness of reducing the main indicators of endogenous intoxication of groups 2 and 3 are presented in Table 4.

Table 4

Indicators of the effectiveness of reducing the main indicators of endogenous intoxication

Indicators	***Upon admission***	***After decompression***	***2 days after PA with IECO***	***2 days after PA with IECO and Ozone***
total protein, g/l	77,3±0,3	76,5±0,2	74,5±0,5	74,6±0,45
urea, mmol/l	16,3±0,8	14,1±0,6	7,2±0,3	7,1±0,3
creatinine, mmol/l	0,2±0,01	0,16±0,01	0,07±0,01	0,07±0,01
total bilirubin, mmol/l	218,2±16,4	197,4±9,8	39,3±2,7	38,1±2,5
alanine aminotransferase	0,96±0,04	0.85±0,03	0,09±0,05	0,09±0,04
aspartate	1,5±0,05	1,3±0,06	0,2±0,08	0,19±0,09
aminotransferase molecules of medium mass, conl. units.	0,85±0,09	0,73±0,08	0,40±0,05	0,39±0,04
total albumin concentration, g/l	38,7±1,4	37,9±1,1	36,3±2,0	36,4±2,1
effective albumin concentration, g/l	18,3±0,5	19,7±0,6	35,2±0,5	35,1±0,5
albumin binding capacity, conl. unit	0,46±0,03	0,53±0,04	0,9±0,07	0.9±0,08
leukocyte intoxication index	3,7±0,01	3,2±0,02	2,8±0,02	2,7±0,03

As can be seen from Table 4, the combination of PA with IECO and additional plasma ozonation was more effective in many parameters, in addition, additional exposure to ozone made it possible to reduce the exposure time from 4-16 (on average from 8-12 hours) to 3-4 hours. The

reliability of the data obtained was checked using the Student's t-criteria P = 0.05 in relation to the initial indicators.

A comparative analysis of laboratory parameters established their normalization in patients of groups 2 and 3 on the 5th-6th day, which corresponds to the optimal timing of the operation.

The greatest number of complications occurred in patients of group 1 (17.7%), in patients of groups 2 and 3 - 9.7% and 8.1%, respectively. The most frequent of them are suppuration of a postoperative wound, acute hepatic-renal insufficiency, cholemic bleeding and peritonitis.

A higher postoperative mortality was found in group 1 (6.4%), which was 2 times higher than this indicator in groups 2 and 3 patients (3.2%). The main cause of death was acute hepatic-renal insufficiency, angiocholitis, and sepsis. In groups 2 and 3, the most severe patients with purulent obstructive cholangitis died. Preliminary decompression and rehabilitation of the biliary tract with plasmapheresis in these patients led to a decrease in deaths and duration of hospitalization by an average of 5-9 days.

In patients with severe endogenous intoxication, in the postoperative period, the most severe endotoxicosis, multiple organ failure persisted in patients of group 1. On the contrary, patients of groups 2 and 3 showed the best results of surgical treatment due to the developed therapeutic and diagnostic algorithm. Thus, differentiated therapeutic and diagnostic tactics in acute cholangitis complicated by biliary sepsis, using a 3-stage method of decompression, plpzmapheresis and sanitation of the biliary tract, is the most rational for this category of patients, which is confirmed by a significant reduction in the number of complications, a decrease in postoperative mortality, acceleration of clinical recovery.

Conclusions:

1. The most informative instrumental and laboratory methods that make it possible to establish the diagnosis and severity of purulent cholangitis at an early stage are: echography of the hepatopancreatoduodenal region in dynamics and ERCPG, the study of bilirubin, blood creatinine, leukocytosis, intoxication indices.

2. The most severe degree of endogenous intoxication was detected in patients who underwent surgery without plasmapheresis sessions, which was accompanied by high mortality (6.4%). Preliminary minimally invasive decompression, a course of detoxification therapy including plasmapheresis, can reduce postoperative mortality by 4 times, the number of complications by 2 times, and accelerate the clinical recovery of patients.

3. The developed differentiated stage-by-stage surgical tactics with the implementation of minimally invasive decompressions and the use of plasmapheresis allows to stop the phenomena of endotoxicosis, cholestasis and liver dysfunction, and thereby improve the results of treatment of patients with acute cholangitis.

4. The proposed method of plasmapheresis is a highly effective method of preoperative preparation in patients with severe cholemic endotoxicosis, contributing to the stabilization of the activity of cytolytic (lowering of alanine aminotransferase and aspartate aminotransferase) and cholestatic (lowering of bilirubin) process, improving the protein-synthetic function of the liver,

allowing to eliminate the main clinical manifestations in this severe contingent of patients and thereby significantly expand indications for surgical treatment.

5. Regeneration of the plasma of patients exfused during plasmapheresis for 3-4 hours with a solution of sodium hypochlorite and additional ozonation reduces its toxicity and makes it suitable for reinfusion into the patient's body. The proposed improved plasmapheresis with reinfusion of extracorporally modified autoplasm reduces the need for donor protein preparations, reduces the risk of possible immune reactions, the risk of infection of the patient with hepatitis B and C viruses, human immunodeficiency virus, cytomegalovirus, herpes virus.

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