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ВЛИЯНИЕ СОРБЕНТА ЛИГНОВА НА КОНЦЕНТРАЦИЮ ИНТЕРЛЕЙКИНА-6 В КРОВИ И ЖЕЛЧИ У ПАЦИЕНТОВ С МЕХАНИЧЕСКОЙ ЖЕЛТУХОЙ ОПУХОЛЕВОЙ ЭТИОЛОГИИ

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ЦЕЛЬ – изучение изменения концентрации IL-6 в крови и желчи у больных механической желтухой (МЖ) опухолевого генеза методом билиарной сорбции.

МЕТОДЫ И МАТЕРИАЛЫ. Исследование проведено с целью изучения изменения концентрации ИЛ-6 в крови и желчи на фоне сорбции желчи у 105 больных механической желтухой (МЖ), причиной обтурации была опухоль периампулярной зоны. Пациенты разделены на 2 группы. Первую группу составил 51 пациент, вторую группу – 54 пациента. Всем больным основной группы с целью декомпрессии была выполнена чрескожная чреспеченочная холангиостомия; Сорбцию желчи проводили с использованием отечественного энтеросорбента «Лигнов». Уровень IL-6 в сыворотке крови и желчи определяли иммуноферментным методом.

РЕЗУЛЬТАТЫ. Использование сорбции желчи в комплексе лечения достоверно изменяло концентрацию IL-6 в сыворотке крови ($P<0,01$) и желчи. Определение ИЛ-6 в крови и желчи позволяет более объективно оценить степень цитокиновой эндогенной интоксикации в ответ на проводимые лечебные мероприятия при опухолях периампулярной зоны, осложненных механической желтухой. Применение сорбции желчи способствует снижению концентрации провоспалительного цитокина IL-6 в крови и желчи как индуктора эндогенной интоксикации и каскада воспалительных процессов у больных с опухолями периампулярной зоны, осложненными механической желтухой.

ЗАКЛЮЧЕНИЕ. Применение сорбции желчи способствует снижению концентрации провоспалительного цитокина IL-6 в крови и желчи как индуктора эндогенной интоксикации и каскада воспалительных процессов.

Ключевые слова: *опухоли билиопанкреатодуоденальной зоны, периампулярные опухоли, механическая желтуха, эндотоксемия, чрескожная чреспеченочная холангиостомия, интерлейкин-6, сорбции желчи*

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THE EFFECT OF LIGNOVA SORBENT TO THE CONCENTRATION OF INTERLEUKIN-6 IN THE BLOOD AND BILE IN PATIENTS WITH MECHANICAL JAUNDICE OF TUMORS ETIOLOGY

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The OBJECTIVE was to study changes of IL-6 concentration in the blood and bile in patients with MJ of tumor genesis by means of biliary sorption.

METHODS AND MATERIALS. The investigation was conducted to study changes in the concentration of IL-6 in the blood and bile against the background of bile sorption in 105 patients with mechanical jaundice (MJ), the cause of obturation was a tumor of the periampullary zone. The patients are divided into two groups. The first group consisted of 51 patients, the second group included 54 patients. All patients of the main group underwent percutaneous

perhepatic cholangiostomy for the purpose of decompression; bile sorption was performed using the domestic Lignov enterosorbent. The level of IL-6 in blood serum and bile was determined by enzyme immunoassay.

RESULTS. The use of bile sorption in the treatment complex significantly changed the concentration of IL-6 in blood serum ($P<0.01$) and bile. Determination of IL-6 in blood and bile makes it possible to more objectively assess the degree of cytokine-induced endogenous intoxication in response to ongoing therapeutic measures for tumors of the periampullary zone complicated by mechanical jaundice. The use of bile sorption contributes to a decrease in the concentration of the pro-inflammatory cytokine IL-6 in the blood and bile as an inducer of endogenous intoxication and a cascade of inflammatory processes in patients with tumors of the periampullary zone complicated by mechanical jaundice.

CONCLUSION. Bile sorption application helps to decrease proinflammatory cytokine IL-6 concentration in blood and bile as an inductor of endogenous intoxication and inflammatory processes cascade.

Keywords: *biliopancreatoduodenal zone tumors, periampulary tumors, mechanical jaundice, endotoxemia, percutaneous transhepatic cholangiostomy, interleukin-6, bilesorption*

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Mechanical jaundice (MJ) implies presence of block in extrahepatic bile ducts preventing outflow of bile from common bile duct into duodenum, which leads to bilirubin accumulation in blood serum and other body fluids, accompanied by specific staining of skin, mucous membranes and sclera of eyes [1, 2]. Among all diseases of hepatopancreatobiliary zone, bile duct obstruction makes up 12–45.2 % [2, 3]. The incidence of benign MJ in worldwide statistics is 4.8–22.5 %, the process occurs acutely due to ducts blockage because of concrements moving, and malignant genesis – 36.6–47 % that occurs gradually due to tumor invasion (bile duct tumors, pancreas head and papilla) [4, 6, 7, 14]. There are also known cases when MJ developed directly because of metastases, in the most cases from cancer of gastrointestinal tract and in more rare cases from ovarian cancer, breast cancer [4, 5].

The leading moments in pathogenesis of hepatic failure and cholangitis are – disruption of hepatic hemodynamics, free radical oxidation of lipids of biomembranes, hepatocyte death, due to the detergent action of bile acids, this in turn triggers apoptosis processes and develops hepatic and multiple organ failure [2, 9]. According to recent data, inhibition of cellular and activation of humoral component of immunity is important in MJ [10]. There is the decreased levels of interleukin-2, increased levels of B-lymphocytes, T-suppressors, immunoglobulins, circulating immune complexes, interleukin-6 (IL-6) [11]. It should be noted that surgery itself induces immunodeficiency state in the body, which is most often manifested by the formation of purulent-septic complications. In patients with MJ and biliary hypertension, an imbalance of pro- and anti-inflammatory cytokines and endogenous intoxication are also aggravated by surgery. This is manifested by a sharp increase in interleukin-6 and 10 concentrations [9, 11]. After performing percutaneous transhepatic cholangiostomy (PCTHChS), to decompress biliary hypertension, the immune function of an organism is restored and cytokine levels normalize [6, 14].

Experimental [8, 12, 13] and clinical [15] studies have shown increased levels of IL-6 in plasma and other cytokines in MJ. According to some data, in patients with tumors, the combination of persistent cytokine increase and prolonged acute phase response is associated with a decrease in protein calorie, leading to surgical complications and death [10, 11].

Endocrine effects occur when cytokines reach target cells circulating with the blood, most commonly TNF-α, IL-1, IL-6, and M-CSF [7].

The occurrence of endotoxemia, bacterial translocation, depression of cellular immunity, and activation of various cytokines, such as IL-6 in MJ, represent a response to systemic inflammation [9, 11, 15].

Analysis of cytokine (IL-6) in biological fluids in primary common bile duct cancer is the main marker in diagnosis and determination of tumor process activity, as well as endogenous intoxication [4, 12].

The persisting tendency of increasing frequency of biliopancreatoduodenal diseases, complicated by cholestasis, high lethality indexes of patients with MJ condition conditions the necessity to study thoroughly all aspects of this form of surgical pathology [1, 13].

The objective was to study changes of IL-6 concentration in blood and bile in patients with MJ of tumor genesis by means of biliary sorption.

Methods and materials. 105 patients with MJ of tumor genesis were studied. Patients were divided into two groups. Jaundice period duration by the moment of hospitalization was on the average 27.9±2.21 days. At the same time in 11 (10.5 %) patients with cholestasis lasted up to 15 days, in 37 (35.2 %) – from 15 to 30 days, in 57 (54.3 %) – more than 1 month.

The first group consisted of 51 patients aged from 33 to 84 years (62.8±2.14), including 33 (64.7 %) male and 18 (35.3 %) female patients in whom IL-6 concentration in blood and bile was measured in dynamics after PCTHChS.

The cause of MJ in 32 (62.7 %) patients was a tumor of pancreatic head, in 11 (21.5 %) – hepatic portal tumor, in 3 (5.8 %) – terminal choledochal tumor, in 5 (9.8 %) – carcinoma of the Faters papilla.

The second group consisted of 54 patients with MJ of tumor genesis in whom bile sorption was performed after PCTHChS. The patients' age varied from 19 to 84 years, on the average 55.5±2.30 years. There were 35 men and 19 women.

The main cause of MJ was a common hepatic duct tumor – in 26 (48.1 %) patients. In 19 (35.2 %) patients cholestasis was

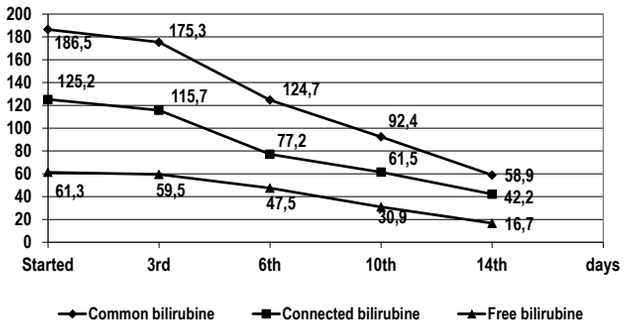

Fig. 1. Serum bilirubin levels in the first group of patients

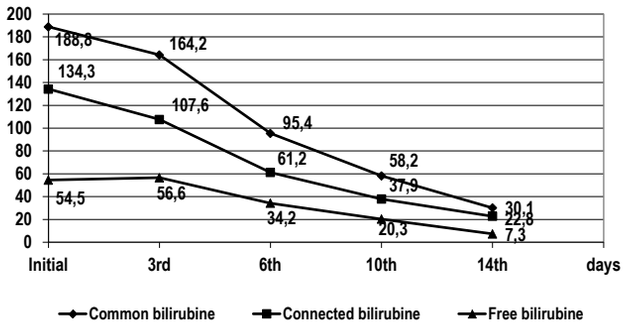

Fig. 2. Serum bilirubin levels in the second group of patients

Table 1

The indicators of biochemical composition of bile in the dynamics in MJ patients of the first group in the period after PCTHChS, n=51

Indicator, mg %	Prak. healthy	After PCTHChS, days				
		1st	3rd	6th	10th	14th
Bilirubin	14.5±0.5	45.2±5.2	61.4±7.2	62.4±5.5	187.5±12.5	91.8±7.3

p<0.001 statistically significant differences.

caused by pancreatic duct head tumor, in 5 (9.3 %) patients – by the tumor of large duodenal papilla, in 4 (7.4 %) – by the tumor of terminal choledochus.

All patients, irrespective of the localization of the tumor process, underwent PCTHChS. Separated bile in the control group was taken orally, without pre-treatment. And in the main group of patients, the separated bile was treated with sorbent Lignova, after which the patients were taken orally.

Concentrations of bilirubin in blood and bile were determined by standard methods. IL-6 level in blood serum and bile was determined by enzyme immunoassay (Vector-Best, Novosibirsk, Russia).

In the second group of patients, biliary absorption was performed using a new domestic enterosorbent Lignova. Lignova is a natural enterosorbent consisting of products of hydrolysis of components of cotton fiber polymer lignin, the structural elements of which are derivatives of phenylpropane and hydrocellulose.

The bile separated by the PCTHChS tube was collected into common hermetically sealed sterile vials and sorbent Lignova was added in the ratio 1:10. Duration of bile sorption was 1 hour. After that, bile was given to the patients to take inside. This way biliary absorption was carried out.

Results. In the first group of patients, the content of total bilirubin in the blood ranged from 79.1 to 335.4 μmol/l, averaging 186.5±5.7 μmol/l. The mean concentration of direct bilirubin was 125.2±7.4 μmol/L, and that of indirect bilirubin was 61.3±4.3 μmol/L. Against the background of transfusion-infusion therapy, the serum total bilirubin content decreased by 61.4 % (*fig. 1*).

Bilirubin is a ballast substance, which has a toxic effect if its content is high in blood serum and bile. On the 3rd day after bile ducts decompression, an increase of bilirubin concentration in bile up to 1.3 times of initial level was registered. Bilirubin concentration in bile remained unchanged till the 6th day, its average value was 608±5.1 mg %.

On the day following the application of PCTHChS, there was an accelerated excretion of bilirubin in the bile. On the 10th day, its content increased 4.1 – fold, the average value being 187.5±12.5 mg %. On the next day, bilirubin concentration tended to decrease on the average to 91.8±7.3 mg % (p<0.001). Bilirubin concentrations, providing bile toxicity, remained at a high level till the end of observation (*table 1*).

The concentration of IL-6 in serum before the application of PCTHChS was higher than normal, averaging 153.7±16.3 pg/ml. Immediately after the application of PCTHChS in bile, the mean value was 69.1±7.3 pg/ml (*table 2*). High IL-6 content in the blood serum and bile testified to the marked endogenous intoxication.

IL-6 concentration decreased to 32.8 % in serum on the first day after application of PCTHChS. The next day, there was little change, but on day 6 of follow-up, there was a slight increase in blood. In bile, IL-6 concentrations fell by 17.3 % over the same period. The values remained practically unchanged until the 6th day of observation. On the 14th day of observation, the decrease of IL-6 level in blood in comparison with the initial level was 63.9 %, and in bile – 53.9 % (p<0.001) (*table 2*).

In the second group of patients, the blood total bilirubin content averaged 188.8±7.2 μmol/l, with variations from 79.1 to 337.9 μmol/l. Hyperbilirubinemia was due to direct fraction to the average of 134.3±6.8 μmol/l and indirect fraction to 54.5±3.2 μmol/l. In 4 patients with MJ duration greater than 40 days, the difference in concentration between bilirubin fractions decreased due to a relative increase in the indirect fraction, indicating a more pronounced liver failure. Bilirubinemia levels above 250.0 μmol/l were detected in 55.8 % of patients (*fig. 2*).

After bile ducts decompression with bile absorption on the 3rd day, serum total bilirubin level had a tendency to decrease on the average: 164.2±5.7 μmol/l. On the 6th day, the level of total bilirubin decreased considerably by 48.8 % from the initial level. In dynamics, improvement of the patients' state of health was noticed, skin pruritus decreased, appetite appeared. On the 14th day of biliary absorption, the concentration of total bilirubin decreased by 84.2 % from the initial level (*fig. 2*).

Table 2

IL-6 concentration in biospecimens in patients with MJ of the first group before and after PCTHChS, n=51

IL-6 pg/ml	Normal	After PCTHChS, days.				
		1st	3rd	6th	10th	14th
Blood	0–10	153.7±16.4	103.4±11.5	111.7±5.6	62.1±4.2	55.1±6.5
Bile	5.4–6.8	69.1±7.3	57.1±4.4	52.1±5.3	35.9±6.2	30.7±6.4

p<0.001 statistically significant differences.

Table 3

The indicators of biochemical composition of bile in the dynamics in patients with MJ of the second group after biliary sorption, n=54

Indicator, mg %	Prak. healthy	Before bile absorption	After bile absorption, days			
			3rd	6th	10th	14th
Bilirubin	14.5±0.5	54.2±6.4	72.3±8.4	115.1±13.7	222.6±24.7	48.4±5.1

p<0.01 statistically significant differences.

Table 4

IL-6 concentration in biological environment of patients with MJ of the second group before and after biliary absorption, n=54

Indicator, mg %	Normal	Before bile absorption	After bile absorption, days			
			3rd	6th	10th	14th
Blood	0–10	152.6±14.3	86.9±9.5	78.7±5.1	47.4±5.4	35.5±4.1
Bile	5,4–6,8	68.5±9.2	42.3±3.4	37.6±4.7	20.8±2.3	16.6±2.7

p<0.01 statistically significant differences.

The composition of the bile after biliary absorption was characterized by a gradual increase in the bilirubin content, especially after 6 days of observation. The maximum occurred on the 14th day (*table 3*).

In this group of patients at baseline, after the application of PCTHChS, the IL-6 concentration in blood serum averaged 152,6±14,3 pg/ml, and in bile it was 68,5±9,2 pg/ml. The inclusion of biliary absorption in the treatment complex significantly changed the IL-6 concentration in blood serum(p<0.01) and bile (*table 4*).

It can be seen from the table, that initially high concentration of IL-6 in blood and bile after bile absorption tended to decrease and at the end of observation, it was reduced by 75.7 % (35.5±4.1 pg/ml) and 73.9 % (16.6±2.7pg/ml) from the initial level, respectively.

Discussion. The analysis of carried out researches shows that traditional treatment at ML decompression doesn't provide the elimination of the factors causing endogenous intoxication, increasing tumor growth and inflammatory process that complicates the preparation of patients with periampulary tumors complicated with MJ, for the second stage of the radical operative treatment after application of PCTHChS. Biliary sorption with the domestic enterosorbent Lignova as a sorbent of endogenous products of intoxication, excreted with bile, helps to eliminate hepatic insufficiency, to restore the basic functions of the liver and to reduce endotoxemia. Application of bile sorption prevents the development of hepatic and renal insufficiency.

The sorption capacity of Lignova with respect to IL-6 was detected and it was 12.4 %. IL-6 glycoprotein with a molecular weight of 19–24 kDa. This protein belongs to the inflammatory cytokines. In our studies, the initial concentration of IL-6 in the blood serum increased on average to 152.4±17.3 pg/ml. In bile, the concentration of this cytokine ranged from 4,.0 to 200.28 pg/ml and averaged 67.48±13.24 pg/ml. The concentration of IL-6 in blood serum and bile was determined before and after decompression of the bile ducts by PCTHChS. The concentration of IL-6 on the initial day after the imposition of PCTHChS in the blood serum decreased to 32.9 %. On the following day, this indicator remained practically unchanged, but on the 6th day of observation, there was the slight increase in it in the blood. In the bile at the same time, the concentration of IL-6 decreased by 17.1 %. These indicators remained practically unchanged up to 6 days of observation. On the 14th day, the decrease in the level of IL-6 in the blood compared to the baseline was 64.4 %, and in the bile 54.3 % (p<0.001).

Comparative evaluation of the results of the study of bile and blood in patients of the control and main groups showed that the use of bile sorption led to the improvement in the chemical composition of bile, the decrease in endogenous intoxication in blood serum and bile, and restoration of the functional state of the liver. The composition of bile after bile sorption was characterized by the gradual decrease in the content of bilirubin, especially after 6 days of observation. The maximum came on the 14th day.

The concentration of bilirubin in bile on the 14th day decreased by 1.3 times (to 48.4±5.1 in the main group

and to 91.8±7.3 mg % in the control group) ($p<0.05$). On the 14th day of bile sorption, the concentration of cholesterol in bile in patients of the main group decreased to 48.1 %, and in the control group to 16.4 %.

In patients of the main group, IL-6 in the blood decreased by 75.7 %, and in the control group – by 64.4 % of the initial level. In bile on the 14th day, the level of IL-6 in patients of the main group decreased by 73.9 %, and in the control group – by 54.3 %.

The comparative study of the results of surgical interventions in patients of the control and main groups showed that in the main group, when using bile sorption, there was more pronounced improvement in biochemical parameters, the decrease in endogenous intoxication than in the control group. The chemical composition of bile was characterized by more significant decrease in the level of bilirubin, which confirms the restoration of the functional state of the liver. Thus, the study of indicators of the composition of bile and endotoxicosis in patients with obstructive jaundice of obstructive genesis with PCTHChS showed that their concentration in bile changes in direct proportion to their concentration in the blood. By the concentration of indicators of endotoxicosis in bile, one can indirectly judge their concentration in the blood.

Conclusion. Thus, determination of IL-6 in blood and bile gives possibility to estimate more objectively a degree of tumorous process and cytokine induced endogenous intoxication on the response of carried out treatment measures at biliopancreatoduodenal tumors, complicated with MJ. Bile sorption application helps to decrease proinflammatory cytokine IL-6 concentration in blood and bile as the inductor of endogenous intoxication and inflammatory processes cascade as well as bilirubin elimination from the body in patients with biliopancreaticoduodenal tumours complicated by MJ.

Conflict of interest

The authors declare no conflict of interest.

Compliance with ethical principles

The authors confirm that they respect the rights of the people participated in the study, including obtaining informed consent when it is necessary, and the rules of treatment of animals when they are used in the study. Author Guidelines contains the detailed information.

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