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THE DYNAMICS OF IMMUNOLOGICAL INDICANTS ON THE BACKGROUND OF THERAPY USING PROBIOTICS AND PSYLLIUM IN PATIENTS WITH CHRONIC PANCREATITIS AFTER CHOLECYSTECTOMY

Summary. The results of complex examination and treatment of 64 patients with chronic pancreatitis after cholecystectomy are given. It is ascertained, that complex therapy with the use of probiotics and psyllium in patients with chronic pancreatitis after cholecystectomy has marked positive effect on dysbiotic changes and immunity indicants (IgA, IgG, IgM, C3, C4) compared to monotherapy with corresponding medications.
Key words: chronic pancreatitis, cholecystectomy, dysbiosis, immunity, treatment.

Actuality of the Problem

Every year nearly 2.5 million cholecystectomies (CE) are done in the world. By the frequency of its performance this surgery is inferior only to appendectomy. According to various sources, complaints of gastroenterological nature occur in 5 to 40 % of patients after CE. Only half of the patients note remission after CE [1].

In 15 to 40 % of cases CE leads to new disease, which is combined into a general complex of symptoms called postcholecystectomical syndrome (PCES), that is manifested by functional disorders of the organs of the digestive system (sphincter of Oddi dysfunction), and also formation of chronic pancreatitis (CP). Often signs of PCES are noted after the removal of a functioning gall bladder (GB) [2].

Functional and organic disorders of the digestive system, observed in 25–60 % of patients after CE, occur as a result of the loss of the physiological role of the gallbladder, sphincter of Oddi dysfunction, disturbance of the bowel passage, enterohepatic circulation of bile acids, as well as changes in the quantitative and qualitative composition of colon microflora [3].

In CP, especially in presence of exocrine pancreatic insufficiency, enteropancreatic syndrome is often formed, which is characterized by disruption of the normal intestinal microbiocenosis with the development of intestinal dysbiosis (ID). If there are dysbiotic changes in patients with CP the enzymatic activity of intestinal microflora becomes one of the important pathogenetic factors of malabsorption and development of diarrhea. This complicates the clinical course of CP, affects the assimilation of nutrients. Violation of intestinal microbiocenosis in patients with CP often cause polynutritional insufficiency syndrome and breach of the trophological status [4].

It is known that a well-functioning intestinal microflora is actively involved in the development of immunobiological reactivity of the organism (the synthesis of immunoglobulins, interferon, maintaining the functional activity of the body's non-specific protective factors) in metabolism, in the synthesis of vitamins, amino acids, etc. [5].

It becomes quite evident that in patients with CP after CE the correction of the quantitative and the qualitative composition of the colon microflora should be conducted in

order to prevent the development of various metabolic and immunological disorders in the organism.

Aim of the research. To study the effectiveness of the complex therapy with the use of probiotics and medication based on Plantago ovata on the dynamics of the colon dysbiosis and immune status indicants in patients with chronic pancreatitis after cholecystectomy.

The scientific research is a fragment of the fiscal topic SR 001134002361, № 829 «Mechanisms for optimizing the diagnosis and treatment of hepatopancreatobiliar zone diseases depending on the influence of exogenous and endoecological environmental factors» that is performed at the departments of surgical diseases and propaedeutics of internal diseases of medical faculty of State higher educational institution «Uzhgorod national university».

Materials and Methods

Under our supervision there were 64 patients receiving inpatient treatment in therapeutic branch of hospital clinic CHC MIA of Ukraine in Transcarpathian region and in the surgical department № 1 of Transcarpathian regional clinical hospital named after A. Novak located in Uzhhorod. Cholecystectomy was conducted on all of the examined in terms of from 2 to 8 years.

All studies were conducted with the consent of patients and the methodology of their conducting was held in the accordance with the Declaration of Helsinki 1975 and its revision in 1983.

Patients were aged from 21 to 65 years, the average age was (42.7 ± 8.2) years, there were 16 males (25.0 %), and 48 females (75.0 %). Cholecystectomy was performed in average (6.01 ± 2.15) years ago.

The control group included 20 almost healthy individuals aged 20 to 63 years, the average age was (40.1 ± 4.6) years. There were 11 men (55.0 %) and 9 women (45.0 %).

General clinical research methods were performed on all the patients before and after the treatment. The diagnosis of CP aggravation was determined considering complaints, anamnesis, laboratory (general analysis of blood and urine, blood chemistry, scatological study). Also, ultrasound of the abdominal cavity was performed on all of the examined patients (the device Philips HDI-1500).

Before and after the treatment stool culture was taken for dysbiosis. At the same time quantitative account of microorganisms grown on nutrient environment of agar, Saburo, Endo and 5% blood agar was conducted per 1 g of stool. In addition, on the cup with 5% blood agar the presence of hemolytic forms of both intestinal and coccal flora, the percentage of the total number of grown colonies, the ratio of the intestinal and coccal microflora was spotted. The presence of bifidobacteria was determined by the nature of growth in the Blaurock's medium and smears microscopy stained by Gram. The number of bifidobacteria and lactobacilli in one gram of stool was determined by limiting dilution at which their growth was observed. The degree of intestinal dysbiosis was evaluated by the classification of I.B. Kuvaeva and K.S. Ladodo (1991).

Before and after the conducted complex treatment the patients with CP after CE had their levels of complement components C3, C4 and concentration of immunoglobulins (Ig) A, M, G determined using chromogenic analysis conducted on the Sysmex 500 and 560 (Japan) apparatus, using Siemens company reagents.

Providing medical care for patients with CP after CE was performed according to clinical treatment protocol of Ministry of Health of Ukraine № 271 dated 13.06.2005 and local protocols. Basic treatment of patients with CP after CE include destination tailor enzyme replacement therapy, antispasmodics, prokinetics, if necessary — non-narcotic analgesics.

Three groups of patients were formed, which differed by the correction mode of colon dysbiosis. The first group of patients (n = 20) with CP after CE received combined probiotic agent rotabiotic — 2 capsules 3 times daily after meals for 14 days, then 1 capsule 3 times daily for 10 days. The second group of patients (n = 20) with CP after CE received the drug of prebiotic action mucofalk — 1 sachet dissolved in 150 ml of water 4 times daily for 3 weeks. For the third group (n = 24) of patients with CP after CE the medical complex was prescribed on the background of the basic therapy, which included rotabiotic and mucofalk for 3 weeks.

The analysis and processing of the patient examination results were carried out with the computer program Statistica (StatSoft Inc., USA). The data obtained was processed using the variation statistic method, taking into account the value of the arithmetic mean and mean error (M ± m) with the assessment of values authenticity according to Student's t-test.

Results of the Studies and Their Discussion

After conducting clinical and laboratory examinations chronic pancreatitis was verified in all of the patients. Anamnesis has shown that the patients didn't misuse alcohol. CP formed on the background of biliary disease (cholecystectomy was performed in all of the patients in terms of (6.01 ± 2.15) years).

Determination of the quantitative and qualitative composition of colon microflora before the treatment indicates dysbiotic changes in the colon in patients with acute exacerbation of chronic pancreatitis. This manifested in the reduction of inoculation frequency and the number of *Bifidobacterium, Lactobacillus, Escherichia, Enterococcus* and the increment of the frequency of detection of *Staphylococcus, Klebsiella, Proteus, Candida* compared with the control group indicants.

Administration of differential treatment schemes for patients with CP after CE had a positive impact on the indicants of microbial composition of the colon. The results obtained in groups of patients are shown in Table 1.

As can be seen by the results of the repeated microbiological examination in patients with CP after CE, the conducted complex therapy has positively influenced the indicants of quantitative and qualitative composition of the colon microflora. Positive dynamic was established in all of the three groups of patients, but more marked changes were observed in patients of the group III (si-

multaneous therapy using rotabiotic and mucofalk). At the same time in all of the patients of the group III normalization of the quantity of Bifidobacteria, Lactobacilli and Escherichia was set. Inclusion of probiotic or psyllium into the treatment complex for patients with CP after CE was effective on correspondent strains of microorganisms only in 90.0–95.0 % of cases. The given changes were accompanied by decrease/normalization of the quantity of *Clostridium* ((4.21 ± 0.11) lg CFU/g), *Citrobacter* ((1.58 ± 0.04) lg CFU/g), *Enterobacter* ((1.35 ± 0.17) lg CFU/g), $p < 0.05$, and *Staphylococcus* ((3.45 ± 0.07) lg CFU/g) in patients of the III group. Positive changes of the given indicants were also observed in patients of group I and II, but less marked, than in the patients of group III.

Positive changes of the quantitative and qualitative composition of colon microflora in patients with CP after CE has also positively influenced the dynamics of immunoglobulins and complement indicants (Table 2).

In patients with CP after CE the reduction of C3 indicants (key link of the complement system) was observed, and increment of IgA and IgG levels, which is the apparent evidence of the activation of organism's immune competent system (its humoral link) in these patients.

After the treatment a more marked positive dynamic of immunological status indicants was observed in patients

Table 1 — Dynamics of qualitative and quantitative composition of colon microflora of the patients with CP after CE on the background of differentiated therapy

Indicant	Group I (n = 20)		Group II (n = 20)		Group III (n = 24)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Bifidobacterium	Control group 100.0 % (8.62 ± 0.14)					
Occurrence (%)	75.0	95.0	80.0	90.0	75.0	100.0
Lg CFU/g	6.07 ± 0.15	6.98 ± 0.23	6.11 ± 0.05	7.21 ± 0.18	6.04 ± 0.15	7.89 ± 0.12
Lactobacillus	Control group 100.0 % (6.83 ± 0.12)					
Occurrence (%)	70.0	100.0*	80.0	95.0	83.3	100.0
Lg CFU/g	5.23 ± 0.19	6.32 ± 0.21	5.36 ± 0.17	6.24 ± 0.23	5.32 ± 0.21	6.52 ± 0.11
Escherichia	Control group 100.0 % (7.93 ± 0.09)					
Occurrence (%)	85.0	95.0	90.0	90.0	79.2	100.0
Lg CFU/g	6.42 ± 0.23	7.11 ± 0.12	6.51 ± 0.07	7.12 ± 0.15	6.32 ± 0.14	7.52 ± 0.19
Enterococcus	Control group 100.0 % (7.52 ± 0.20)					
Occurrence (%)	45.0	80.0*	40.0	75.0	41.7	83.3*
Lg CFU/g	6.02 ± 0.04	7.11 ± 0.24	6.10 ± 0.09	6.99 ± 0.15	6.12 ± 0.21	7.55 ± 0.05*
Enterobacter	Control group 25.0 % (1.12 ± 0.07)					
Occurrence (%)	60.0	40.0	55.0	35.0	62.5	29.2*
Lg CFU/g	2.92 ± 0.09	1.23 ± 0.14	2.89 ± 0.06	1.77 ± 0.14	3.01 ± 0.05	1.35 ± 0.17*
Citrobacter	Control group 45.0 % (1.42 ± 0.07)					
Occurrence (%)	25.0	35.0	25.0	40.0	20.8	45.8*
Lg CFU/g	2.45 ± 0.08	1.75 ± 0.21	2.45 ± 0.27	1.87 ± 0.09	2.52 ± 0.12	1.58 ± 0.04*
Staphylococcus	Control group 35.0 % (3.23 ± 0.11)					
Occurrence (%)	55.0	35.0	65.0	40.0	66.7	37.5
Lg CFU/g	4.77 ± 0.31	3.89 ± 0.14	4.82 ± 0.12	3.99 ± 0.15	4.75 ± 0.16	3.45 ± 0.07
Klebsiella	Control group 20.0 % (1.01 ± 0.04)					
Occurrence (%)	50.0	35.0	45.0	30.0	50.0	25.0*
Lg CFU/g	3.71 ± 0.17	1.89 ± 0.05*	3.88 ± 0.21	2.01 ± 0.17*	3.86 ± 0.10	1.41 ± 0.06*
Clostridium	Control group 15.0 % (4.19 ± 0.16)					
Occurrence (%)	40.0	30.0	40.0	35.0	41.7	20.8*
Lg CFU/g	5.44 ± 0.37	4.48 ± 0.12	5.31 ± 0.09	4.52 ± 0.15	5.41 ± 0.17	4.21 ± 0.11
Proteus	Control group 10.0 % (0.31 ± 0.04)					
Occurrence (%)	35.0	25.0	40.0	35.0	37.5	16.7
Lg CFU/g	2.54 ± 0.08	1.11 ± 0.15	2.44 ± 0.15	1.12 ± 0.09	2.39 ± 0.14	0.85 ± 0.19*
Candida	Control group 10.0 % (3.23 ± 0.22)					
Occurrence (%)	25.0	15.0	20.0	10.0	25.0	12.5*
Lg CFU/g	4.61 ± 0.15	3.85 ± 0.15	4.47 ± 0.11	3.66 ± 0.15	4.31 ± 0.27	3.44 ± 0.16

*Note. Differences between indicants before and after treatment are accurate: * — $p < 0.05$.*

Table 2 — Dynamics of indicants of humoral link of immunity in patients with CP after CE

Indicant, g/l	Group I (n = 20)		Group II (n = 20)		Group III (n = 24)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
IgA	11.44 ± 2.15	7.89 ± 1.01*	12.05 ± 2.14	8.01 ± 0.75*	11.78 ± 1.99	5.55 ± 0.52*
IgM	5.89 ± 0.12	4.77 ± 0.14	5.74 ± 0.16	4.52 ± 0.25	5.92 ± 0.85	3.52 ± 0.41
IgG	24.52 ± 1.10	18.45 ± 0.84	23.75 ± 1.40	19.26 ± 1.02	24.77 ± 1.12	16.41 ± 1.11*
C3	0.75 ± 0.04	1.10 ± 0.05	0.81 ± 0.02	1.0 ± 0.07	0.79 ± 0.04	1.41 ± 0.01*
C4	0.14 ± 0.05	0.19 ± 0.01	0.16 ± 0.05	0.20 ± 0.05	0.15 ± 0.02	0.29 ± 0.04

*Note. Differences between indicants before and after treatment are accurate: * — p < 0.05.*

with CP after CE of group III, although it should be emphasized that positive tendency in the dynamics of immunoglobulins and complement indicants was determined in groups I and II.

In all of the three patient groups a positive tendency toward normalization of IgA was determined (up to (7.89 ± 1.01) g/l in group I; up to (8.01 ± 0.75) g/l in group II; up to (5.55 ± 0.52) g/l in group III, $p < 0.05$). However, normalization of IgG was observed only in the third group of patients (up to (16.41 ± 1.11) g/l) while conducting treatment with the use of probiotic and psyllium. Statistically significant difference in C3 indicants before and after the treatment were also observed only in the third group of patients (from (0.79 ± 0.04) g/l to (1.41 ± 0.01) g/l, $p < 0.05$).

Thus, the correction of dysbiotic changes of the colon in patients with CP after CE promotes normalization of immunological disorders in the body.

For the correction of intestinal dysbiosis in patients with CP after CE the combination of rotabiotic and mucofalk has proven to be more effective, than monotherapy with corresponding medications. Simultaneous use of the combined probiotic agent rotabiotic, which consists of lyophilized bacteria $2.5 \cdot 10^9$ CFU: *Lactobacillus bulgaricus* — $0.5 \cdot 10^9$ CFU, *Streptococcus thermophilus* — $0.8 \cdot 10^9$ CFU, *Lactobacillus acidophilus* — $0.8 \cdot 10^9$ CFU, *Bifidobacterium* ssp. (*Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis*) — $0.4 \cdot 10^9$ CFU; inulin — 150.0 mg and mucofalk (seeds of Plantago ovata) has also proven to me more effective on the dynamics of immunological indicants in patients with CP after CE.

It is known, that after taking mucofalk acidification of the intestinal environment is observed, which itself leads to growth inhibition of pathogenic microorganisms, which in its turn creates more optimal conditions for action of bacteria that are part of the rotabiotic. The drug with prebiotic action mucofalk has significant anti-inflammatory effect and absorbent effect in relation to pathogenic microorganisms [6], which also stimulate effects of rotabiotic. With this comes a faster normalization of bifido- and lactoflora of the colon, which have high immunogenic properties, manifested primarily in maintaining the concentration of IgA.

Analysis of the results indicates the normalization of IgG and complement C3 on the background of reducing the severity of dysbiotic changes in patients with CP after CE. In patients with CP after CE intestinal dysbiosis should be corrected, which helps normalize immunological changes in these patients and may underlie the prevention of progression of disease manifestations.

Therefore, studies allow us to recommend probiotic agent rotabiotic and prebiotic agent mucofalk to normalize intestinal dysbiosis and immunological indicants in patients with CP after CE.

Conclusions

In patients with chronic pancreatitis after cholecystectomy dysbiotic changes in the colon and activation of humoral immunity link are determined.

The complex therapy with the use of probiotic and prebiotic medication psyllium leads to normalization of quantitative and qualitative composition of the colon microflora, and this, respectively — to the positive dynamics of immunological homeostasis indicants in patients with chronic pancreatitis after cholecystectomy.

References

1. Губергриц Н.Б. Холецистэктомия и сфинктер Одди: как достигнуть консенсуса? / Н.Б. Губергриц, Г.М. Лукашевич, О.А. Голубова, П.Г. Фоменко // Сучасна гастроентерологія. — 2013. — № 1 (69). — С. 55-65.

2. Шевченко Б.Ф. Дифференцированный подход к органосохраняющим операциям в лечении желчнокаменной болезни / Б.Ф. Шевченко, А.М. Бабий // Гастроэнтерология. — 2013. — № 3. — С. 95-101.

3. Madacsy L. Characterization of functional biliary pain and dyspeptic symptoms in patients with sphincter of Oddi dysfunction: effect of papillotomy / L. Madacsy, R. Fejes, G. Kurucsai // World J. Gastroenterol. — 2006. — № 12 (42). — P. 6850-6856.

4. Бабінець Л.С. Вплив супутнього хронічного обструктивного захворювання легень на стан мікробіоценозу товстого кишечника і клінічний перебіг хронічного панкреатиту / Л.С. Бабінець, О.С. Квасніцька // Кримський терапевтичний журнал. — 2009. — № 1. — С. 59-61.

5. Preidis G.A. Targeting the Human Microbiome With Antibiotics, Probiotics, and Prebiotics: Gastroenterology Enters the Metagenomics // Gastroenterol. — 2009. — № 136. — P. 2015-2031.

6. Полевая Е.В. Энтеросорбционные свойства псиллиума (Мукофалька®) и возможные механизмы его действия при кишечных инфекциях / Е.В. Полевая, Т.Я. Вахитов, С.И. Ситкин // Клинические перспективы гастроэнтерологии, гепатологии. — 2012. — № 2. — С. 1-4.

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ДИНАМИКА ИММУНОЛОГИЧЕСКИХ ПОКАЗАТЕЛЕЙ НА ФОНЕ ТЕРАПИИ С ИСПОЛЬЗОВАНИЕМ ПРОБИОТИКОВ И ПСИЛЛИУМА У БОЛЬНЫХ С ХРОНИЧЕСКИМ ПАНКРЕАТИТОМ ПОСЛЕ ХОЛЕЦИСТЭКТОМИИ

Резюме. Приведены результаты комплексного обследования и лечения 64 больных хроническим панкреатитом после холецистэктомии. Установлено более выраженное положительное действие на дисбиотические изменения и показатели иммунитета (IgA, IgG, IgM, C3, C4) комплексной терапии с использованием пробиотика и псиллиума у больных с хроническим панкреатитом после холецистэктомии по сравнению с монотерапией соответствующими препаратами.

Ключевые слова: хронический панкреатит, холецистэктомия, дисбиоз, иммунитет, лечение.

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ДИНАМІКА ІМУНОЛОГІЧНИХ ПОКАЗНИКІВ НА ФОНІ ТЕРАПІЇ ІЗ ВИКОРИСТАННЯМ ПРОБІОТИКІВ ТА ПСИЛІУМУ У ХВОРИХ ІЗ ХРОНІЧНИМ ПАНКРЕАТИТОМ ПІСЛЯ ХОЛЕЦИСТЕКТОМІЇ

Резюме. Наведено результати комплексного обстеження та лікування 64 хворих на хронічний панкреатит після холецистектомії. Установлена більш виражена позитивна дія на дисбіотичні зміни та показники імунітету (IgA, IgG, IgM, C3, C4) комплексної терапії з використанням пробіотика та псиліуму у хворих на хронічний панкреатит після холецистектомії порівняно з монотерапією відповідними препаратами.

Ключові слова: хронічний панкреатит, холецистектомія, дисбіоз, імунітет, лікування.