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**ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE**

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ANALYSIS OF IMMEDIATE AND REMOTE RESULTS OF TRADITIONAL
TREATMENT METHODS AND THE CHRONOLOGY OF RECURRENCE OF CROHN'S
DISEASE

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✓ *Resume*

Traditional approaches to the treatment of Crohn's disease in 57.1% of cases are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results. Relapse of Crohn's disease with traditional approaches to the treatment of the disease is noted in 59.5% of cases.

Key words: Crohn's disease, treatment, relapse.

АНАЛИЗ НЕПОСРЕДСТВЕННЫХ И ОТДАЛЕННЫХ РЕЗУЛЬТАТОВ
ТРАДИЦИОННЫХ МЕТОДОВ ЛЕЧЕНИЯ И ХРОНОЛОГИИ РЕЦИДИВА БОЛЕЗНИ
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✓ *Резюме*

Традиционные подходы при лечении болезни Крона в 57,1% случаев сопровождаются с развитием послеоперационных осложнений, среди которых преобладают парастомальные виды (33,3%) и раневая инфекция (25%), приводящие к высокой частоте (31%) неудовлетворительных непосредственных результатов лечения. Рецидив болезни Крона при традиционных подходах к лечению заболевания отмечается в 59,5% случаев.

Ключевые слова: Болезнь крона, лечение, рецидив.

KRON KASSALLIGINI ANANAVIY USULDA DAVOLASHDAN SONGI YAKIN VA UZOK MUDDATLI NATIJALARINING TAHLILI VA KASSALLIK QAYTALANISHI XRONOLOGIYASI

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✓ Rezyme

Kron kasalligini davolashning an'anaviy yondashuvlari 57,1% hollarda operatsiyadan keyingi asoratlarning rivojlanishi bilan birga keladi, ular orasida parastomal turlari (33,3%) va yara infeksiyasi (25%) ustunlik qiladi, bu esa qoniqarsiz davolash natijalarining yuqori chastotasiga (31%) olib keladi. Kasallikni davolashning an'anaviy yondashuvlari bilan Crohn kasalligining qaytalanishi 59,5% hollarda kuzatiladi.

Kalit so'zlar: Kron kasalligi, davolash, qaytalanish

Relevance

To date, it has already been proven that the pathogenesis of Crohn's disease (CD) is based on the body's immune response to tissue inflammation due to exposure to luminal bacterial antigens (1,3,5). The main participants in the immune response are subpopulations of T and B lymphocytes that enter the intestine during the development of CD [2,4,6,15].

The pathogenesis is also supported by the interaction of these cells with integrins, adhesion molecules, and multiple chemokines responsible for the production of elevated levels of pro-inflammatory and anti-inflammatory cytokines, which are the target of immune and non-immune cells and contribute to mucosal inflammation.

Dysregulation of various components of the immune system is invariably found in the mucous membrane of patients with CD. The most pronounced change is the hyperactivity of T cells with excessive cytokine production, between which IL-12 and INF- γ , which contribute to the Th1 lymphocytic type phenotype, in contrast to Th2, which correlate with ulcerative colitis. In addition, TNF- α production has been shown to increase the number of CD4+ FoxP3+ T-regulatory cells, especially in the mucous membrane of children with Crohn's disease [7,9]. Inhibition of effector cytokines such as TNF- α attenuates deleterious effects in subgroups of CD patients [8,10,16,17].

Further analysis of T cell subpopulations revealed the presence of Th1 and Th17 cells in CD, while the cytokines considered more involved are TNF, IL-12 and IL-23. In addition to cytokines, IL-34 is also associated with inflammatory bowel diseases and, in particular, with CD [11,13,18].

From the very beginning of surgical treatment of Crohn's disease, there was no consensus on the optimal procedure. Surgical resection of the diseased intestine has become the procedure of choice for the majority of patients with terminal ileum CD or with ileocolitis, including in complicated cases [14,15].

The term "recurrence" is used to define the appearance of new lesions after intestinal resection. Active monitoring for early diagnosis of relapses is considered mandatory. A wide range of diagnostic measures is used for this purpose. However, most of them: endoscopy, ultrasound examination of the intestine, including using contrast, etc. refers to routine clinical research methods. Currently, treatment methods that take into account other pathogenetic links in the development of CD are vague and are devoted to various comparative studies in the general system of inflammatory bowel diseases.

The purpose of the study: To study the unsatisfactory results of traditional treatment methods with an analysis of the causes of crohn's disease recurrence.

Material and methods

The results of a comprehensive examination and treatment of 82 patients with Crohn's disease (CD) were analyzed. The patients were divided into 2 study groups: the control group (42 patients) and the main group (40 patients). A distinctive feature of the patient groups was the use of different approaches in predicting and preventing CD recurrence. As reference values, 20 healthy individuals were examined, who were recognized as practically healthy by the medical commission. Male patients prevailed in the control and main groups of patients (59% and 55%, respectively), and the average age varied between young and middle (according to the WHO classification).

CD mainly affected the terminal ileum (61%). Combined lesions of the terminal ileum and large intestine were diagnosed in 24.4% of patients. Isolated colon lesion was diagnosed in 14.6% of patients. In each study group, patients with lesions of the terminal ileum prevailed. Perianal lesions were more characterized by the presence of rectal fistulas (75%), anal fissures (37.5%), narrowing of the lower ampullary rectum (8.3%), strictures of the anal canal (4.2%) and long-term non-healing wounds (4.2%).

The chronology of the course of the disease depended on the affected part of the intestine in CD. Thus, it took the least amount of time to damage the terminal part of the ileum (89.7 ± 13.4 months). For the development of CD with damage to the large intestine, the course of the disease was on average for 121.3 ± 33 months. Combined lesions of the terminal ileum and colon were diagnosed in patients with a CD history of 179.8 ± 43.8 months.

Among the surgical operations in the anamnesis, appendectomy should be distinguished, which was performed in 9 (21.4%) patients of the control group and in 15 (37.6%) patients of the main group. Operations aimed at opening acute paraproctitis were performed significantly more often (in the control group 35.7% of cases and in the main group of patients in 40% of cases, respectively). The list of operations also included excision of pararectal fistulas (in the control group 16.7% of cases and in the main group of patients in 22.5% of cases, respectively), excision of rectal fissures (in the control group 11.9% of cases and in the main group of patients in 15% of cases, respectively), diagnostic laparotomy (in the control group 7.1% cases and in the main group of patients in 15% of cases, respectively) and laparoscopy (in the control group 14.3% of cases and in the main group of patients in 20% of cases, respectively).

In 54.9% of cases, patients had previously received hormone therapy, while steroid resistance was diagnosed in 53.7% of cases.

In 84.1% of cases, patients were diagnosed with chronic continuous CD. Chronic recurrent course of the disease was detected in 12.2%. The acute course of CD was diagnosed in 3 (3.7%) patients.

The study design was based on an open, cross-sectional retrospective and prospective cohort study.

All the patients included in the study were operated on by us for complications of CD

Instrumental diagnostic methods were performed without fail. The entire range of instrumental research methods included the following methods: ultrasound examination of the abdominal cavity and perineum; multispiral computed tomography with intravenous contrast and enterography; magnetic resonance imaging of the abdominal cavity according to individual indications with questionable MSCT data; video colonoscopy with mandatory examination of the Baugin flap and terminal ileum. This made it possible to assess the degree of CD development using a simple endoscopic scale (SES-CD).

When assessing the immediate results of treatment, we used a scale developed by A.O. Okhunov and A.D. Sapaev (2018). According to this method, a distinction was made between good, satisfactory and unsatisfactory immediate treatment results.

CD recurrence was determined by the appearance of typical symptoms of the disease in clinical remission, spontaneous or medically supported.

The severity of CD recurrence was determined according to the criteria of the Society for the Study of Inflammatory Bowel Diseases at the Association of Coloproctologists of Russia (2009).

The results and their discussion

Traditional approaches to Crohn's disease treatment in the form of surgical interventions included ileocecal resection of the intestine (22 patients; 52.4%), resection of part of the ileum (15 patients; 35.7%), coloproctectomy with Brooke ileostomy (3 patients; 7.1%) and subtotal resection of the colon with ileosigmoid anastomosis (2 patients; 4.8%). In 12 (28.6%) patients, jejunum segments were also resected.

Infiltrates of the abdominal cavity were detected in 26 (61.9%) patients, with 14 (53.8%) of them having intestinal fistulas intraoperatively. Intestinal fistulas in 64.3% of cases (9 patients) had the character of a pathological connection between the terminal ileum and the ascending colon, and in the remaining 35.7% of cases (5 patients) – between the terminal ileum and the sigmoid colon.

When the formed fistulas were eliminated, 11 (78.6%) patients underwent fistula suturing with a defect in the intestinal wall, and 3 (21.4%) patients underwent resection of the affected intestinal area with the formation of a colorectal anastomosis.

Formed abdominal abscesses were detected in 4 (9.5%) patients who had an infiltration in the abdominal cavity in the preoperative period.

In most cases (54.8%), the operation was completed by removing the intestinal stoma. Ileoascendostomy (39.1%) and double-stemmed ileostomy after primary intestinal anastomosis (34.8%) were among the leading options. In 6 (26.1%) patients, the operation was completed with a single-barrel ileostomy.

In other cases, intestinal resection resulted in the formation of an anastomosis without a preventive stoma.

The immediate treatment results were evaluated chronologically up to the 14th day of the postoperative period. Subsequently, according to the timing of the study, the incidence of Crohn's disease recurrence in the long-term postoperative period was assessed.

The feeling of well-being during the 1-7-day postoperative period was assessed by 27 (64.3%) patients to a greater extent as average, which was associated with the persistence of moderate (77.8%) or severe (22.2%) abdominal pain. 40.7% of patients had nausea, and 18.5% had flatulence. 14 (33.3%) patients reported poor general health. And only 1 (2.4%) patient felt well. The low percentage of the patient's well-being was also associated with the volume of surgery performed and the short duration of the postoperative period. We deliberately focus on this fact, since already on the 14th day of the postoperative period, the number of patients with good health increased to 15 (35.7%). The number of patients with average (35.7%) well-being decreased significantly (by 2 times less) and the number of patients with poor health decreased slightly (to 28.6%).

Within 1-7 days after surgery, the frequency of stools per day averaged 3.14 ± 0.79 times, while in the following 8-14 days this indicator decreased to 2.82 ± 0.34 times per day. Stool frequency was calculated in patients with a colostomy bag after colostomy or ileostomy was performed as needed to change the colostomy bag. In the early postoperative period, the stool was often liquid.

The average body temperature in the first week after surgery for Crohn's disease fluctuated at a subfebrile level and amounted to 37.94 ± 3.16 °C. This level of the average body temperature was taken into account in the calculation even if antipyretic drugs were used when body temperature reached a febrile level. As the treatment progressed, the body temperature decreased and averaged 37.28 ± 2.28 °C. At the same time, in 28.7% of patients, body temperature had not increased at all by this time.

The heart rate on the first day of the postoperative period averaged 85.96 ± 12.18 beats per minute, and in the period from 8 to 14 days - 75.14 ± 9.81 beats per minute.

Laboratory blood tests revealed mainly an increase in hemoglobin and the level of total protein in the blood against the background of a decrease in the rate of erythrocyte sedimentation and the concentration of C-reactive protein (Table 1). We noted postoperative complications in 24 (57.1%) patients with Crohn's disease, and according to the Clavien-Dindo classification, they were distributed as follows: Grade I – 11 (26.2%) patients; grade II – 6 (14.3%) patients; IIIa – 4 (9.5%) patients and IIIb – 3 (7.1%) patients.

Postoperative complications in 19% of cases (8 patients) were characterized by the development of various parastomal functional and structural (marginal necrosis, bleeding, infiltration, etc.) disorders. This type of complication turned out to be the most frequent among the operated patients for Crohn's disease.

Table 1

Dynamics of changes in laboratory blood parameters in assessing the immediate results of Crohn's disease treatment

Indicators	DYNAMICS OF THE EARLY POSTOPERATIVE PERIOD	
	1-7-days	8-14- days
Hemoglobin (g/l)	$85,96 \pm 27,47$	$105,42 \pm 8,51$
Erythrocyte sedimentation rate (mm/hr)	$14,43 \pm 2,26$	$12,84 \pm 1,76$
C-reactive protein (mg/l)	$21,53 \pm 4,56$	$13,76 \pm 2,59$
Total protein in blood (g/l)	$53,18 \pm 12,08$	$58,47 \pm 9,19$

Wound infection developed in 6 (14.3%) patients, and 5 patients also had an infiltrate of the abdominal cavity. An abscess of the small pelvis was formed in 3 (7.1%) patients, and 1 patient (2.4%)

each had to develop anastomotic suture failure, as well as perforation of an acute ulcer of the small intestine. In this case, the patient required repeated surgical intervention.

Performing a sigmoidrectal anastomosis against the background of a purulent-inflammatory process in the abdominal cavity, as well as the presence of prolonged hormone therapy, led to the development of a postoperative complication.

In general, good results were found in 12 (28.6%) cases in the immediate postoperative period among patients in the control group, satisfactory treatment results in 17 (40.5%) cases, and unsatisfactory treatment results in 13 (31%) cases.

We found a recurrence of Crohn's disease among patients in the control group in 25 (59.5%) patients. At the same time, in 31% of cases (in 13 patients), it manifested itself only by an increase in the average frequency of stools (up to 4 times a day) in the absence of deviations in other clinical and laboratory parameters.

Recurrence of Crohn's disease in 21.4% of cases (9 patients) was manifested by increased stool frequency up to 6 times a day, the addition of moderate abdominal pain, subfebrile body temperature and slight weight loss. There were no hemodynamic disorders in such patients.

The average hemoglobin level in the blood was 95.4 ± 5.5 g/l, ESR was 22.8 ± 7.3 mm/h, and the number of leukocytes in the blood was $7.9 \pm 2.1 \times 10^9/l$. The average C-reactive protein did not exceed 10 g/l, and the total protein level was 52.4 ± 4.5 g/l (Table 2).

In 3 (7.1%) patients, Crohn's disease recurrence was more severe in the form of increased stool frequency more than 7 times a day with severe abdominal pain and periodic febrile body temperature. Hemodynamic changes in these patients were manifested by increased pulse rate on average 115.8 ± 5.1 times per minute. The average hemoglobin level in the blood was 72.6 ± 4.6 g/l, the ESR was 34.5 ± 4.3 mm/h, and the number of leukocytes in the blood was $14.8 \pm 3.6 \times 10^9/L$. The average C-reactive protein exceeded 10 g/l, and the total protein level was 48.3 ± 3.1 g/l.

Table 2

Dynamics of changes in laboratory blood parameters in the assessment of long-term results of Crohn's disease treatment

indicators	DYNAMICS OF THE LONG-TERM POSTOPERATIVE PERIOD		
	30-days	90- days	180- days
Hemoglobin (g/l)	$117,1 \pm 13,7$	$95,4 \pm 5,5$	$72,6 \pm 4,6$
ESR (mm/hr)	$6,1 \pm 3,2$	$22,8 \pm 7,3$	$34,5 \pm 4,3$
C-reactive protein (mg/l)	$3,25 \pm 0,3$	$8,17 \pm 1,2$	$28,44 \pm 4,1$
Total protein in blood (g/l)	$64,6 \pm 5,8$	$52,4 \pm 4,5$	$48,3 \pm 3,1$

The chronology of Crohn's disease recurrence was characterized by its development starting from the 14th day of the postoperative period (2.4%). The maximum peak of Crohn's disease recurrence occurred between 100 and 180 days of the postoperative period.

Thus, in 57.1% of cases, traditional approaches to the treatment of Crohn's disease are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results. The recurrence of Crohn's disease with traditional approaches to the treatment of the disease is noted in 59.5% of cases, mainly occurring in mild and moderate type (88%). The chronology of the increase in the incidence of Crohn's disease recurrence is directly proportional to the increase in the duration of the postoperative period.

Conclusions

1. Traditional approaches in the treatment of Crohn's disease in 57.1% of cases are accompanied by the development of postoperative complications, among which parastomal types (33.3%) and wound infection (25%) prevail, leading to a high frequency (31%) of unsatisfactory immediate treatment results.
2. The recurrence of Crohn's disease with traditional approaches to the treatment of the disease is noted in 59.5% of cases, mainly occurring in mild and moderate type (88%). The chronology of the increase in the incidence of Crohn's disease recurrence is directly proportional to the increase in the duration of the postoperative period.

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