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ABSTRACT

THE ROLE OF CYTOKINES IN THE DIAGNOSIS AND SURGICAL TREATMENT OF DESTRUCTIVE CHOLECYSTITIS

Specialty: 3213.01 – Surgery

Field of science: Medicine

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Baku – 2024

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"16" 11 2024 il

GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance of the topic: Studies revealed that 20% of the elderly population develops gallstone disease. More than 20% of these patients have complications. The main risk factors of the disease are female sex, patient's age, pregnancy, hypodynamia, obesity, and overeating[1].

Despite the positive prognosis of the disease, if appropriate diagnostic and therapeutic measures are not taken, high morbidity and mortality may result [2]. It is estimated that among elderly patients and patients with complications, mortality reaches 13% and morbidity reaches 40%[3].

In some cases, it is also possible that acute cholecystitis turns into complicated cholecystitis, leading to bleeding, gangrenous forms, and perforation. However, it is difficult to predict the complications of cholecystitis in a specific case[4].

Despite the continuous improvement of the diagnostic criteria of gallstone disease and the great development of treatment methods, there is no decrease in the development of complications of the disease[5].

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According to modern surgical requirements, surgical intervention should be preferred in the treatment of patients with various forms of cholecystitis. In modern times, laparoscopic cholecystectomy is considered the "gold standard" in the surgical treatment of gallstone disease[6].

It is known that early cholecystectomy allows patients to reduce their financial expenses significantly. However, the transition to open surgery, as well as the increase in complications and the inflammatory process, require special attention to these patients[7].Opinions differ regarding the initiation of surgical treatment in acute gallstone disease. There are supporters of early treatment, as well as supporters of conservative treatment before surgery[8].

Although many studies have been conducted, the role of cytokines in the gallbladder and their effect on gallstone formation is not fully understood[9].

It has been shown that the improvement of diagnostic and therapeutic approaches in the treatment of gallstone diseases should be based on the main pathogenesis of gastrointestinal tract pathologies[10].

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One of the main reasons for the occurrence of purulent-inflammatory complications after surgery related to gallstone disease is serious changes in the immune system of patients, in the functional activity and number of immune component cells. In the development of the inflammatory process and in the pathogenesis of infection after surgical intervention, the characteristics of the human body, immune reactivity in general, as well as their interaction, are of great importance[11].

The balance of cytokines is disturbed in patients with calculous cholecystitis. This is associated with infection of the blood, development of endogenous intoxication and disruption of the functional parameters of internal organs[12].They also provide interactions and relationships of the immune system with various organs and systems of the body. Thus, cytokines have a certain role in the pathogenesis of cholecystitis and immunopathologies. All this shows that applying immunocorrective treatment in the pre- and post-operative periods by studying the nature of immune reactivity disorders in determining the severity of cholecystitis is of scientific and practical importance. Cytokines, enzymes, exchange products, and other biochemical factors are of particular importance in the development of pathogenetic treatment principles and in the evaluation of the short-term and long-term effects of the disease.

Thus, there is no doubt that the study of indicators of immune reactions, as well as cytokines, regulation with immunomodulators in different periods of treatment of patients with destructive cholecystitis

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is a promising direction in improving the results of the treatment of the disease.

The object of the study. The object of the study was 104 patients with a confirmed diagnosis of destructive cholecystitis (86 in the main group and 18 in the comparison group) and 14 healthy individuals admitted to the Educational-Surgical Clinic of the Azerbaijan Medical University during 2016-2019.

The purpose of the research. Preoperative study of cytokines in blood samples of patients with destructive cholecystitis for diagnostic purposes and improvement of disease treatment results by applying immunomodulators in complex treatment after surgery.

The research tasks:

1. Based on the comparative analysis of the pre-operative cytokine profile with other laboratory indicators in patients with destructive cholecystitis, the study of the necessity of applying an immunomodulator in the complex treatment after the surgery
2. Studying the dynamics of changes in biochemical laboratory analysis indicators between the comparison group and the main group after surgery in patients with destructive cholecystitis
3. A study of the dynamics of changes in cytokine indicators in the comparison group and the main group after surgery in patients with destructive cholecystitis
4. A study of the dynamics of changes in immunoglobulin indicators in the comparison group and the main group after surgery in patients with destructive cholecystitis

Research methods

- clinical examinations;
- biochemical examinations;
- immunological examinations;
-instrumental examinations;
-mathematical-statistical analysis methods.

Scientific novelty of the study:

- In patients with destructive cholecystitis, the use of immunomodulators after surgery is justified based on the changes in the dynamics of cytokine status before surgery

- A significant positive change in the immune status and cytokine indicators was noted by applying an immunomodulator in the complex treatment

Practical significance of the study:

1. Comprehensive study of the state of the immune system and documentation of the immunological profile in patients with destructive cholecystitis, who underwent cholecystectomy, created new diagnostic possibilities.
2. The application of immunotherapy in the complex treatment after the surgery made it possible to improve the outcomes of the disease.

The main provisions of the dissertation presented to the defense:

1. In patients with destructive cholecystitis, the study of the cytokine profile together with detailed biochemical examinations has an important role in clarifying the clinical diagnosis and choosing treatment tactics.
2. In patients with destructive cholecystitis, it is more appropriate to combine the Imunofan drug with the preventive and therapeutic measures provided in the protocol.

Approbation of the research. The results of the research were reported at the following conferences:

International Scientific and Practical Conference "Science and Education in the XXI Century", Tombov, September 30, 2021;

International scientific forum "Science and Innovation - Modern concepts", Moscow, October 22, 2021;

" XVIII International Euroasian Congress of Gastroenterology and Surgery", September 11-14, 2019.

The results of the research were reported and discussed at the AMU interdepartmental meeting on March 10, 2021 (meeting No. 08).

Publications. The results and fragments of the dissertation are represented in 4 theses and 12 articles.

Application of research results. The results of the dissertation were included in the scientific plan of the Surgical Clinic of the Azerbaijan Medical University.

Organization where the dissertation was performed. The research was performed at the base of the Educational - Surgical Clinic of the Azerbaijan Medical University.

The structure and volume of the dissertation. The dissertation has a volume of 157 computer typing pages (194 728 characters) consisting of an introduction (7350 characters), Chapter I (60153 characters), Chapter II a description of the research materials and methods (23921 characters), Chapter III dedicated to the personal research (49726 characters), Chapter IV (23804 characters), Conclusion (27190 characters), Results (2242 characters), Practical recommendations (342 characters) and Bibliography. The results of the dissertation are visualized through 21 tables, 19 graph and 6 picture the bibliography contains 192 sources.

MATERIALS AND METHODS

The amounts of various enzymes were determined in blood samples of 104 patients with a confirmed diagnosis of destructive cholecystitis, (86 patients in the main group and 18 patients in the comparison group) and 14 healthy persons and a comparative analysis was performed. Patients admitted to the Educational - Surgical Clinic of the Azerbaijan Medical University during 2016-2019 were involved in the research.

Of the main group of patients, 67 (64.4%) were female and 37 (35.6%) were male. Patients were included in the following age groups: 18-25, 26-40, 41-60, and 61-75 years old. The age distribution of the disease was determined by patients included in the study groups. Thus, only 4 patients aged 18-25 were registered among the patients who underwent cholecystectomy (n=104). This includes 3.8% of the relevant contingent. The number of patients who were included in the age range of 26-40 years for which we had to perform the analogous operation was 26 and it was 25% of the total contingent. The number of patients who were included in the age range of 41-60 years for which we had to perform the analogous operation was 49 and it was 47.1% of the total contingent. The number of cholecystectomy patients

whose ages ranged from 61 to 75 was 25, which means 24.1% of the total cholecystitis patients involved in the study. In general, during the analysis of cholecystectomy patients involved in the study (n=104) by age groups, the highest rate was recorded in 47.1% of people between the ages of 41 and 60. From this point of view, age groups ranging from 61 to 75 and 26 to 40 years of age were monitored.

Apparently, local peritonitis was the most frequent complication in patients with cholecystitis, which agrees with the results of other scientific studies reflected in literature sources.

Cholecystectomy was subsequently performed in patients with cholecystitis according to the instructions. Open laparoscopic surgery was performed on 48 (46.2%) patients and closed laparoscopic surgery on 56 (53.8%) patients.

The causes of cholecyst in the patients included in the study were analyzed. Phlegmon was found in 86 (82.6%) of 104 patients and gangrene in 18 (17.4%) patients.

After the patients were first divided into groups by age and gender, the frequency of occurrence of various concomitant diseases among them was determined. No complications were recorded in 86 (82.6%) patients who underwent cholecystectomy (n=104). The remaining 18 (17.4%) had various complications before surgery. 13 of these patients had symptoms of local peritonitis, 2 had partial intestinal obstruction, and 3 had mechanical jaundice, which included 12.5%, 1.9%, and 3.0% of cholecystitis patients included in the general study, respectively.

Among the causes of cholecystitis in the patients involved in the study, phlegmanous form was more prevalent in 86 (82.6%) and gangrenous form in 18 (17.4%) patients.

In 104 patients with destructive cholecystitis included in the study, biochemical indicators, cytokine profile, and immunoglobulins were examined before surgery.

The laboratory examinations of all patients showed no significant changes in ALT, AST, GGT indicators, but there were significant changes in indicators such as CRP, IL-1, IL-6, TNF-α, and IgA. While the CRP index was high in 86 out of 104 patients, increases in IL-1,

IL-6, TNF- α, and IgA indicators in those patients also attracted attention. Although CRP did not change at high levels in 18 patients, it was found that indicators such as IL-1, IL-6, TNF-a and IgA were not at high limits. In this regard, patients were divided into two groups. Thus, for 86 patients included in the main group, the high CRP limit was assumed to be higher than 17 mg/l, and IL-1, IL-6, TNF-a, and IgA limits higher than 13 pg/ml. These patients received complex treatment, with mandatory use of the immunomodulating drug Immunofan in the postoperative period. In the comparison group, for 18 patients the limit of CRP was assumed to be 12-17 mg/l, and for IL-1, IL-6, TNF-a, and IgA indicators, it was 12 pg/ml, and these patients were treated with traditional conservative treatment in the postoperative period (Figure).

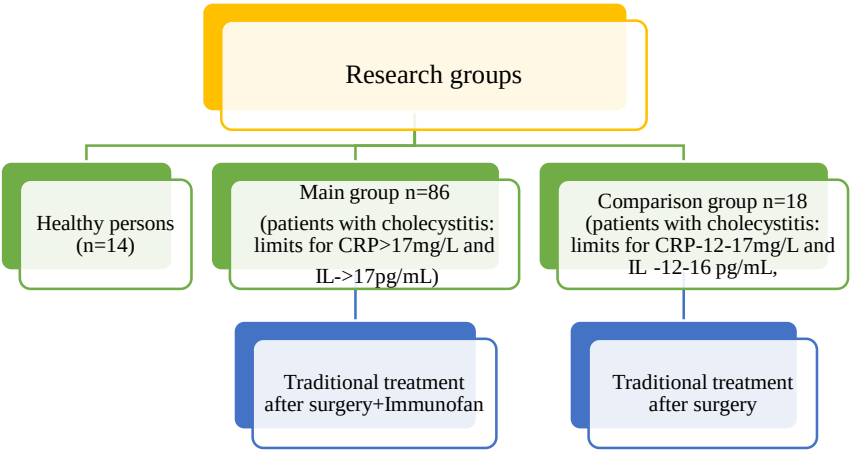

Figure. Design of the research

All patients were examined before treatment, 1, 5 and 10 days after treatment: clinical examination, instrumental examination (chest X-ray, ultrasound examination of abdominal organs, electro-cardiography); biochemical analysis of blood (ALT, AST, GGT, amylase enzymes, albumin, creatinine, cholesterol, total bilirubin,

conjugated bilirubin, and unconjugated bilirubin); immune tests (IL-1, IL-4, IL-6, IL-10 and TNF-α; IgA, IgG and IgM).

The levels of IL-1, IL-4, IL-6, IL-10 and TNF-α cytokines, IgA, IgM, and IgG immunoglobulins in the blood of healthy persons and patients with surgical pathology, included in the study contingent, were examined using the immunoenzyme method.

The concentrations of IL-1, IL-4, IL-6, IL-10, and TNF-α cytokines in blood serum were determined by the solid-phase immunoenzyme variant of the "sandwich" method with mono- and polyclonal antibodies against cytokines using the reagent kit of the company "Vector-Best" (Russian Federation).

The levels of IgA, IgM, and IgG in the blood serum of healthy individuals and patients were determined using the reagent kit of the company "Vector-Best" (Russian Federation).

Immunoenzyme tests were performed on the Stat Fax Plus (USA) immunoenzyme analyzer (ƛ=450 mm, differential filter 650 nm).

The concentration of indicators reflecting the functional state of the liver, bile ducts and pancreas and the activity of enzymes in the blood of practically healthy persons involved in the study and patients with surgical pathologies were examined by biochemical methods. The amounts of albumin, creatinine, cholesterol, CRP, bilirubin and its fractions, as well as the activities of ALT, AST, GGT, and amylase enzymes were determined by colorimetric and kinetic methods using reagent kits of the company "Human" (Germany) in serum obtained after centrifugation of the blood samples taken from the elbow vein on an empty stomach.

Laparoscopic cholecystectomy is considered to be a safe and effective surgical intervention method used in acute cholecystitis. In modern times, the application of new technologies, the development of surgery, and the widespread of endovideosurgical technologies have expanded the possibilities of reliable laparoscopic diagnosis and treatment in abdominal cavity organs. Thus, there is no need for a large laparotomy incision, the operation is performed under more favorable conditions, the frequency of postoperative complications is lower, the

length of stay in the hospital and rehabilitation is shorter, and the costs of treatment are reduced.

Intraoperative dangerous complications are recorded in 1.07% of cases. To ascertain whether the laparoscopy was effective or not, it is sufficient to wait 72 hours.

In the main group, open laparoscopy was performed on 48 (46.2%) patients and closed laparoscopy on 56 (53.8%) patients.

In cholecystectomy patients, Imunofan was injected for 10 days, including the day of surgery.

The obtained data were processed by statistical methods taking into account modern requirements. For the initial assessment of the difference between the variational ranks, the Student's t-test parametric method, the mean difference between the selected indicators for paired related variants and the assessment of the difference between parts were used. Non-parametric criteria - Mann-Whitney U Test and Pearson's $\chi 2$ test were used for verification and refinement of the results.

RESULTS OF PERSONAL RESEARCH

Biochemical monitoring of the condition of patients with cholecystitis allows us to reveal the mechanisms of disease development. This is of great importance in the objective assessment of the severity of endogenous intoxication and in predicting the end of the disease.

Taking these into account, we assessed the functional activity of the liver, pancreas, and bile ducts by determining biochemical indicators before surgery.

Before treatment, the mean value of ALT in the main group (63.5±1.1 V/l) was statistically significantly higher than in healthy individuals (22.9±1.4 V/l) ($t=22.5$ and $p< 0.001$). Before surgery, the level of ALT in the main group was significantly higher than in the comparison group ($t=2.22$, $p<0.05$).

Table 1

Quantification of biochemical indicators at different periods before treatment in research groups and healthy individuals

Parameters	Main group (n=86)	Comparison group (n=18)	Healthy individuals
ALT	63.5±1.1	56.6±2.9	22.9±1.4
AST	56.4±1.2	57.2±2.6	21.6±1.9
ALP	256.7±6.3	221.3±16.2	176.6±11.8
GGT	33.5±0.7	35.9±1.5	21.4±2.2
Amylase	105.7±1.6	81.2±5.2	60.8±3.9
Albumin	35.4±0.2	33.4±0.6	42.6±0.9
Creatinine	108.3±1.4	96.7±4.9	84.5±3.3
Cholesterol	256.8±3.1	240.5±9.1	184.6±6.7
CRP	18.9±0.4	12.3±0.6	3.60±0.3
Total bilirubin	17.9±0.2	14.9±0.9	12.6±0.3
Conjugated bilirubin	5.63±0.1	6.55±0.5	2.71±0.1
Unconjugated bilirubin	12.95±0.2	10.9±0.4	10.54±0.3

The level of AST before treatment was higher in the main group (56.4±1.2 V/l) than in healthy persons (21.6±1.9 V/l), but the difference between the indicators was not statistically significant. Before treatment, the level of AST was statistically significantly higher in the main group compared to the comparison group (57.2±2.6 V/l) ($t=0.28$, $p<0.05$). Before treatment, the level of ALP was statistically significantly higher in the main group (256.7±6.3 IU/L) compared to healthy persons (176.6±11.8 IU/L) ($t=6.0$, $p<0.001$). There was no statistically significant difference in the level of ALP between the main group and the comparison group before treatment. The level of GGT in the main group was statistically significantly lower than that of healthy individuals ($t=5.3$, $p<0.001$). In the comparison group, it was higher than in the main group, but the difference was not statistically significant ($t=1.45$, $p>0.05$). The level of amylase was statistically significantly higher in the main group

(105.7±1.6 V/l) compared to healthy individuals (60.8±3.9 V/L) (t=10.7, p<0.001). Before treatment, the level of amylase was lower in the comparison group than in the main group and the difference was statistically significant (t=4.50, p<0.001). The level of albumin before treatment was statistically significantly lower in the main group (35.4±0.2 V/l) than in healthy persons (42.6±0.9 U/l) (t=8.0, p<0.001). Before the treatment, the amount of albumin in the comparison group was statistically significantly higher compared to the main group (t=3.30, p<0.01). Creatinine level was statistically significantly higher in the main group (108.3±1.4 IU/L) compared to the control group (84.5±3.3 IU/L) (t=6.6, p<0.001). It was statistically significantly higher in the main group than in the comparison group (96.7±4.9 mg/dl) (t=2.27, p<0.05). The mean level of cholesterol before treatment was statistically significantly higher in the main group (256.8±3.1 mg/dl) compared to the control group (184.6±6.7 mg/dl) (t=9.8, p<0.001).

Pronounced, statistically significant differences between groups were found in the level of CRP. Before treatment, the level of CRP in the main group was statistically significantly higher than in the comparison group. Statistical significance t=30.6, p<0.001 was calculated in the main group (18.9±0.4 mg/l) compared to healthy individuals (3.60±0.3 mg/l). It was statistically significantly higher in the main group than in the comparison group (12.3±0.6 mg/l) (t=9.17, p<0.001).

Significant changes occurred also in the amount of bilirubin. Total bilirubin before treatment was statistically significantly higher in the main group (17.9±0.2 μmol/l) than in healthy persons (12.6±0.3 μmol/l) (t=13.2, p<0.001). Before treatment, the total bilirubin level in the main group was statistically significantly higher than that of the comparison group (t=3.26, p<0.01).

The level of conjugated bilirubin was statistically significantly higher in the main group than in healthy individuals (t=29.2, p<0.001). Before treatment, it was higher in the main group than in the comparison group but not statistically significant (t=1.84, p>0.05 (6.55±0.5 μmol/l). The amount of unconjugated bilirubin was

statistically significantly higher in the main group (12.95±0.2 μmol/l) compared to healthy individuals (10.54±0.3 μmol/l) (t=8.0, p<0.001) and the comparison group (10.9±0.4 μmol/l) (t=5.12, p<0.001).

Thus, negative dynamics were observed in all biochemical parameters in the main group before treatment compared to healthy individuals, and the differences in the change of all parameters were statistically significant. Although there were changes in biochemical parameters in the comparison group of patients with destructive cholecystitis, there were no statistically significant differences compared to the healthy group.

In the next stage of the research, the biochemical indicators obtained in the main group were analyzed with respect to the indicators of the comparison group, i.e. patients who underwent cholecystectomy and received traditional treatment in the post-surgery period. We evaluated the functional activity of the liver, pancreas, and bile ducts by determining biochemical indicators in different periods after the operation.

The level of ALT was statistically significantly higher in the main group (70.4±1.0 V/l) compared to the comparison group (58.7±2.5 V/l) one day after surgery (t=4.35 p<0.001). The level of ALT in the main group also decreased 5 days after treatment in both groups. The level of ALT in the main group (40.3±0.4) was statistically significantly lower than in the comparison group (44.5±1.6 V/l) (t=1.09 p>0.05). However, on the 10th day after the operation, the level of ALT in the main group was significantly lower than in the comparison group, but this change was not statistically significant (t=1.09, p>0.05). Thus, the decrease in the level of ALT in the main group can be evaluated as a very positive dynamic.

The level of AST was statistically significantly lower in the main group (53.2±2.3 V/l) compared to the comparison group (65.3±0.9 V/l) on the 1st day after treatment (t=4.90, p<0.001). On the 5th day of treatment, this parameter in the main group (39.7±0.4 V/l) was statistically significantly lower than in the comparison group (41.0±1.6 V/l) (t=0.79, p<0.05). Although AST levels decreased in both groups on day 10 after treatment, this decrease in the main group

(20.4±0.4 V/l) was statistically more significant than in the comparison group (22.6±2.1 V/l), (t=1.03, p>0.05).

Table 2

Biochemical indicators in research groups in different periods after surgery

Groups	ALT	AST	ALP	GGT	Amylase
Before surgery:					
Comparison group	56.6±2.9	57.2±2.6	221.3±16.2	35.9±1.5	81.2±5.2
Main group	63.5±1.1	56.4±1.2	256.7±6.3	33.5±0.7	105.7±1.6
1 day after surgery:					
Comparison group	58.7±2.5	53.2±2.3	231.0±8.4	33.3±1.3	95.4±5.2
Main group	70.4±1.0	65.3±0.9	279±6.4	36.8±0.4	107.3±1.8
5 days after surgery:					
Comparison group	44.5±1.6	41.0±1.6	198.6±5.8	27.0±1.2	74.2±3.2
Main group	40.3±0.4	39.7±0.4	245±5.1	25.6±0.3	75.2±1.3
10 days after surgery:					
Comparison group	25.4±1.4	22.6±2.1	138.1±6.5	19.4±0.8	56.2±2.8
Main group	23.8±0.4	20.4±0.4	182±3.6	22.7±0.4	67.8±1.1

Significant changes in alkaline phosphatase (ALP) levels occurred in both groups after treatment. However, on the first day of treatment, it decreased from 256.7±6.3 IU/l to 279±6.4 IU/l in the main group. Whereas, it increased from 221.3±16.0 IU/l to 231.0±8.4 in the comparison group. Differences in the ALP levels between both groups were not statistically significant. On the 5th day of treatment, the differences between the main group (245±5.1 IU/l) and the comparison group (198.6±5.8 IU/l) were not statistically significant. Even on the 10th day of treatment, statistical significance was not detected between these indicators. However, in the main group, this

parameter (182±3.6 IU/l) remained relatively higher than in the comparison group (138.1±6.5 IU/l).

One day after the treatment measures, a decrease in the limits of GGT was also observed. However, it was statistically significantly higher in the main group (36.8±0.4 IU/l) than in the comparison group (33.3±1.3 IU/l) ($t=2.57$, $p<0.05$). After 5 days of treatment, the GGT was already lower in the main group (25.6±0.3 IU/l) than in the comparison group (27.0±1.2 IU/l), but the decrease was not statistically significant ($t=1.17$, $p > 0.05$). Only on the 10th day of treatment, the limit of GGT was statistically significantly lower in the main group than in the comparison group ($t=3.67$, $p<0.01$).

Positive dynamics in amylase level changes were also detected after treatment measures. Although there was a decrease in the main group (107.3±1.8 U/l) on the 1st day of treatment, it was statistically significantly lower in the comparison group (95.4±5.2 U/l) ($t=2.16$, $p <0.05$). On the 5th day of treatment, it was lower in the comparison group (74.2±3.2 U/l) than in the main group (75.2±1.3 U/l), but statistical significance was not recorded. Although there was a decrease on the 10th day of treatment in both groups, it was still statistically significantly lower in the comparison group (56.2±2.8 U/l) than in the main group (67.8±1.1 U/l) ($t= 3.87$, $p<0.01$).

Besides, to determine the effectiveness of the treatment measures, we examined the dynamics of the changes in the protein metabolism indicators, such as albumin, creatinine, cholesterol, and CRP.

There were significant changes in albumin levels in the research groups after treatment. 1 day after treatment, the albumin level was statistically significantly higher in the main group (39.5±0.2 g/l) than in the comparison group (37.4±0.6 g/l) ($t=3.50$, $p<0.01$). 5 days after the treatment, the difference between the groups (main group – 40.8±0.2, comparison group 40.5±0.5 g/l) was very slight, and statistical significance was not observed ($t=0.90$, $p>0.05$). On the 10th postoperative day, the albumin level increased statistically significantly in the main group (43.2±0.3 g/l) compared to the comparison group (41.7±0.2 g/l) ($t=4.17$, $p< 0.001$).

Special statistically significant differences were also found in the level of creatinine. Thus, in the pre-treatment period, this parameter was statistically significantly higher in the main group than in the comparison group ($t=2.27$, $p<0.05$). On the first day after treatment, the level remained higher in the main group (103.2±1.1 μmol/l) compared to the comparison group (91.9±1.0 μmol/l) ($t=3.5$ $p<0.01$). On the 5th day after treatment, the creatinine level was significantly higher in the main group (76.0±1.9 μmol/l) compared to the comparison group (96.4±0.8 μmol/l), but the difference was not statistically significant ($t= 0.90$, $p>0.05$). On the 10th day after treatment, the creatinine level remained statistically significantly higher in the main group (92.6±0.7 μmol/l) compared to the comparison group (71.8±1.3 μmol/l) ($t=14.05$, $p<0.001$) (Table 3).

Table 3

Changes in protein metabolism indicators in research groups in different periods after surgery

Indicators	1 day after surgery		5 days after surgery		10 days after surgery	
	Comp. group	Main group	Comp. group	Main group	Comp. group	Main group
Albumin	37.4± 0.6	39.5± 0.2	40.5± 0.5	40.8 ±0.2	41.7± 0.2	43.2± 0.3
Creatinine	91.9± 1.0	103.2± 1.1	76.0± 1.9	96.4± 0.8	71.8± 1.3	92.6± 0.7
Cholesterol	225.0± 5.8	298.4± 4.2	192.5± 5.8	225.4± 2.9	149.5± 3.9	190.5± 1.5
CRP	15.3± 1.1	15.4± 0.4	12.8± 0.5	8.5± 0.2	8.0± 0.5	4.2± 0.1

Although positive dynamics were detected in the blood cholesterol level in the groups, it was observed that it remained at a higher level in the main group. Before treatment, cholesterol levels in the main group were statistically significantly higher than in the comparison group ($t=1.70$, $p>0.05$). Although there was a significant reduction after treatment in both groups, the reduction in the

comparison group was statistically significant. On the 1st day of treatment, the cholesterol level was 298.4±4.2 mg/dl in the main group and 225.0±5.8 mg/dl in the comparison group ($t=1019$, $p<0.001$). On the 5th day, cholesterol level was 225.4±2.9 mg/dl in the main group and in the comparison group, it was 92.5±5.8 mg/dl ($t=5.08$, $p<0.001$). On the 10th day, this parameter was 190.5±1.5 mg/dl and 149.5±3.9 mg/dl ($t=9.81$, $p<0.001$), in the main and comparison groups, respectively. Thus, although there was a decrease in the level of cholesterol in the main group, it remained significantly higher than in the comparison group.

Marked, statistically significant differences were found in the level of CRP between groups. On the first day of treatment, the level of CRP was higher in the main group (15.4±0.4 mg/l) than in the comparison group (15.3±1.1 mg/l), but the difference was not statistically significant ($t=0.08$, $p>0.05$). However, 5 days after treatment, the decrease in the level of CRP was prominent in the main group (8.5±0.2 mg/l) compared to the comparison group (12.8±0.5 mg/l ($t=7.96$, $p<0.001$) and after 10 days, the decrease in this parameter was (4.2±0.1 mg/l) also more marked than in the comparison group (8.0±0.5 mg/l) ($t=7.60$, $p<0.001$). This is reflected in the high effectiveness of the Imunofan drug.

In this regard, the inclusion of the Imunofan drug in the post-operative complex treatment measures is of particular importance.

Among the biochemical parameters, we determined total bilirubin (TB), conjugated bilirubin (CB), and unconjugated bilirubin (UB) fractions.

Significant changes also occurred in the amount of bilirubin. The total bilirubin level in the main group before treatment was statistically significantly higher than that of the comparison group ($t=3.26$, $p<0.01$). In the main group, TB was statistically significantly higher even after 1 day of treatment. Although the level was high even after 5 days of treatment, it was not statistically significant ($t=1.60$, $p>0.05$). However, after 10 days of treatment, this increase was still statistically significant ($t=7.75$, $p<0.001$).

Although the level of conjugated bilirubin was lower in the main group before treatment and 1 day after treatment than in the comparison group, the difference was not statistically significant. After 5 days of treatment, this reduction was statistically significant in the main group ($t=6.40$, $p<0.001$). Although there was a reduction 10 days after treatment, the difference was not statistically significant ($t=0.25$, $p>0.05$). The level of UB, which is considered a toxin accumulated in the liver, was also higher in the main group before treatment ($t=5.12$, $p<0.001$). The level remained statistically significantly higher on the 1st ($t=3.87$, $p<0.001$), the 5th ($t=13.7$, $p<0.001$) and the 10th post-treatment days ($t=8.77$, $p<0.001$).

Thus, based on the results, there are many positive aspects of the inclusion of the Imunofan drug in the complex treatment measures prescribed to the patient directly after the operation, which are manifested in the dynamics of various biochemical parameters. Although the levels of liver enzymes such as ALT and AST were statistically significantly higher in the main group before treatment, they decreased statistically significantly as a result of the effect of post-treatment measures. CRP, which is considered an informative biochemical marker of inflammation in the body, decreased statistically significantly after treatment in all three phases.

Thus, the inclusion of the Imunofan drug in the post-operative complex treatment measures of patients with destructive cholecystitis allows biochemical markers to change intensively in positive dynamics and to be statistically significantly restored compared to patients receiving standard treatment.

The activity of the inflammatory process is considered an informative marker used in the diagnosis of many diseases. Diagnostic approaches to its assessment are different, but general trends toward the development and improvement of methods with high sensitivity and specificity are observed. One of these methods is the study of the cytokine profile in the development dynamics of pathology, which is an inflammatory component. Acute destructive cholecystitis is characterized by a very high amount of anti-inflammatory cytokines (TNF-a, IL-1b, IL-10) with a peak concentration on the 1st-2nd days

after surgery, which leads to the initiation of a systemic inflammatory response ("cytokine storm") and indicates the development of polyorgan failure and purulent-septic complications. Correlation between the investigated cytokines and the main markers of endotoxicosis was also revealed.

Changes in pro-inflammatory cytokine IL-6 during acute calculous cholecystitis and anti-inflammatory IL-4 during chronic calculous cholecystitis have diverse characteristics at the local and systemic levels. Determination of the level of these interleukins, along with TNF-α, is considered one of the more informative criteria in the postoperative period.

The effect of the Immunofan drug on the amount of interleukin fractions such as IL-1, IL-4, IL-6, IL-10, and TNFα in blood samples of patients diagnosed with destructive cholecystitis and healthy individuals was determined before surgery (Table 4).

Table 4

Quantitative indicators of cytokines and immunoglobulins in different periods after treatment in patients with destructive cholecystitis

Parameters	Main group (n=86)	Comparison group (n=18)	Healthy individuals
IL-1	13.8±0.2	10.4±0.9	3.35±0.4
IL-4	5.95±0.1	6.1±0.4	3.8±0.4
IL-6	15.5±0.4	12.2±0.8	3.27±0.3
IL-10	17.0±0.3	12.6±0.8	13.2±1.0
TNF-α	16.7±0.4	11.7±1.0	4.2±0.3
IgA	13.0±0.1	5.91±0.4	1.6±0.2
IgG	14.0±0.2	11.6±0.8	11.5±0.7
IgM	1.62±0.04	2.13±0.09	1.08±1.0

From the results of the authors, it is known that the activity of IL-1 is the surrogate of CRP, which is an inflammatory marker. Inflammation is a crucial factor in changing aerobic capacity, and IL-1 is actively involved in this process. The results of the study show

that the level of IL-1 in the main group was statistically significantly lower than in the comparison group before treatment ($t=2.44$, $p<0.05$). After treatment, this indicator continued to increase in the comparison group and remained statistically significantly higher than in the main group ($t=4.28$, $p<0.001$). Interestingly, 5 days ($t=10.67$, $p<0.001$) and 10 days ($t=7.75$, $p<0.001$) after the treatment, this increase was observed with greater intensity in the comparison group, while it was getting lower with the same intensity in the main group and the differences were considered statistically significant.

Involved in limiting the inflammatory response, IL-4 regulates the severity of tissue damage by attenuating pro-inflammatory cytokines.

In our study, in the main group before treatment, IL-4 was found to be lower than in the comparison group, but the differences were not statistically significant ($t=0.37$, $p>0.05$). On the first day after treatment, this indicator was lower in the main group, but no statistically significant difference was observed. The period when IL-4 was statistically significantly lower in the main group was the 5th day of treatment ($t=2.00$, $p<0.05$). The reduction continued on the 10th day of treatment, but again no statistically significant difference was detected ($t=0.50$, $p>0.05$).

Hematopoiesis and chronicization processes are influenced by the multifunctional IL-6, which is also involved in immune reaction mechanisms during the acute phase. In this regard, its role is very important in chronic inflammatory patients.

In our study, before treatment, the level of IL-6 in the main group was significantly higher than in the comparison group ($t=0.37$, $p>0.05$). Such a slightly higher level was also observed on the first day after treatment ($t=0.20$, $p>0.05$). Only on the 5th day of treatment, a statistically significant decrease of IL-6 was observed in the main group ($t=2.00$, $p<0.05$). This can be evaluated as a manifestation of the significant effect of the Immunofan drug on the immune system. The reduction process continued on the 10th day of treatment, but there was still no statistically significant difference ($t=0.50$, $p>0.05$).

Differences were also observed in the level of IL-10, whose main physiological function is to reduce inflammation. IL-10 inhibits the excessive synthesis of pro-inflammatory cytokines.

Before treatment, this indicator in the main group was statistically significantly high ($t=5.18$, $p<0.001$). Even on the 1st ($t=10.6$, $p<0.001$), 5th ($t=6.12$, $p<0.001$) and 10th ($t=12.38$, $p<0.001$) days after treatment, such statistically significant high indicators indicate that the use of the Immunofan drug leads to the rapid reduction of the inflammatory process. TNF-α (tumor necrosis factor) is a crucial cytokine that stimulates the expression of immune components necessary for the regulation of inflammation and tissue damage. TNF-α is expressed as the main inflammatory mediator responsible for the activation of the immune system in infectious processes. Bacterial agents and many other stimuli induce TNF-α synthesis, activating neutrophils, macrophages, and lymphocytes in damaged tissues.

TNF-α level was statistically significantly lower in the main group before treatment ($t=6.36$, $p<0.001$). Such a decrease was also observed on the 1st ($t=2.16$, $p<0.001$), 5th ($t=8.0$, $p<0.001$) and 10th ($t=8.20$, $p<0.001$) days after treatment.

Thus, we found that in the background of treatment with Immunofan, the inflammatory process was attenuated and tissue damage was regulated, and its elimination process was more intensive.

By determining the level of immunoglobulins in different periods before and after treatment in the study groups, we evaluated the effect of the Immunofan drug on humoral immunity.

Immunoglobulins or antibodies consisting of glycoproteins synthesized by plasma cells are one of the most necessary factors of humoral immunity and provide protection against all types of pathogens. Five immunoglobulin classes (G, M, A, E, and D) have been identified in humans. When immunocompetent cells are in initial contact with foreign bodies, the synthesis of specific M immunoglobulins takes place, and then, under the influence of T-cells and B-cell cytokines, they switch to the synthesis of G immunoglobulins and others.

Currently, the main task of IgA is to strengthen local immunity, prevent the adhesion of microorganisms to the mucous membrane, block surface bacterial adhesions and enhance phagocytosis. In this regard, the high level of IgA in both groups before treatment and after treatment attracts attention. The research shows that the IgA level of the main group of patients before treatment was statistically significantly lower than that of the comparison group ($t=3.87$, $p<0.001$). Such a statistically significant reduction continued on the 1st ($t=7.47$, $p<0.001$), 5th ($t=10.2$, $p<0.001$), and 10th days ($t=13.0$, $p<0.001$) after treatment. G immunoglobulins play a key role in the formation of the human body's defense against the invasion of pathogenic microorganisms and foreign bodies; its biological function is to initiate the process of adsorption of pathogens that have entered the human body. Another important biological role of IgG is the activation of the complement system.

In our study, the level of IgG in the main group was statistically significantly higher than in the comparison group ($t=3.00$, $p<0.01$), before treatment. Although its level remained higher compared to the comparison group on the 1st day after treatment, the difference was not statistically significant ($t=1.6$ $p>0.05$). On the 5th ($t=4.33$, $p<0.001$) and 10th ($t=8.41$, $p<0.001$) days after treatment, the level of IgG in the main group was statistically significantly higher.

As the study revealed, the level of IgM in the main group before treatment was lower than that of the comparison group ($t=5.10$, $p<0.001$). The decrease was statistically significant on the 1st ($t=9.80$, p), 5th ($t=7.18$, $p<0.001$), and 10th ($t=2.70$, $p<0.05$) days after treatment.

Comparative analysis of post-treatment biochemical parameters in research and healthy groups.

The obtained results show that although the patients of the main group with destructive cholecystitis had a worse condition before treatment than healthy individuals and the patients of the comparison group, in the post-treatment period, a fairly noticeable positive dynamic was observed in the biochemical parameters, even in some parameters, these differences were more pronounced.

Table 5

Quantitative indicators of biochemical parameters in patients with destructive cholecystitis and healthy individuals 10 days after treatment

Parameters	Main group (n=86)	Comparison group (n=18)	Healthy individuals
ALT	23.8±0.4	25.4±1.4	22.9±1.4
AST	20.4±0.4	22.6±2.1	21.6±1.9
ALP	182±3.6	138.1±6.5	176.6±11.8
GGT	22.7±0.4	19.4±0.8	21.4±2.2
Amylase	67.8±1.1	56.2±2.8	60.8±3.9
Albumin	43.2±0.3	41.7±0.2	42.6±0.9
Creatinine	92.6±0.7	71.8±1.3	84.5±3.3
Cholesterol	190.5±1.5	149.5±3.9	184.6±6.7
CRP	4.2±0.1	8.0±0.5	3.60±0.3
Total bilirubin	12.9±0.1	9.8±0.4	12.6±0.3
Conjugated bilirubin	2.95±0.03	3.0±0.2	2.71±0.1
Uncongugated bilirubin	10.51±0.1	7.0±0.4	10.54±0.3

The average level of ALT changed in the postoperative periods, and on the 10th day in the main group (23.8±0.4) and in the comparison group (25.4±1.4), it remained slightly higher than in healthy individuals, and the difference was not statistically significant.

The average level of AST was lower in the main group (20.4±0.4) than in the comparison group (22.6±2.1) and healthy persons (21.6±1.9). Although this difference was not statistically significant, it attracted attention. The lowest level of ALP after treatment was found in the comparison group (138.1±6.5), but the difference was not statistically significant. The lowest level of GGT was detected in the comparison group (19.4±0.8).

The level of albumin was higher in the main group (43.2±0.3 g/l) than in the comparison group and healthy individuals. However, the difference was not statistically significant.

Thus, as a result of the prescription of Imunofan to patients with severe destructive cholecystitis, the changes in the necessary biochemical parameters were very close to the indicators of healthy individuals, and AST was even lower.

Comparative analysis of post-treatment immune parameters in research and healthy groups. 10 days after the treatment, positive dynamics were observed in the changes of cytokine and immunoglobulin concentrations in the main and comparison groups. However, these changes were more prominent in the main group of patients compared to the healthy group (Table 6).

Table 6

Quantitative indicators of cytokines and immunoglobulins in patients with destructive cholecystitis and healthy individuals, 10 days after treatment

Parameters	Main group (n=86)	Comparison group (n=18)	Healthy individuals
IL-1	5.4±0.1	8.5±0.4	3.35±0.4
IL-4	2.1±0.1	4.5±0.4	3.8±0.4
IL-6	5.8±0.2	9.5±0.4	3.27±0.3
IL-10	6.5±0.3	9.4±0.3	13.2±1.0
TNF-α	5.3±0.2	9.4±0.4	4.2±0.3
IgA	1.9±0.03	3.2±0.1	1.6±0.2
IgG	6.6±0.2	6.9±0.4	11.5±0.7
IgM	1.05±0.02	1.32±0.08	1.08±1.0

Thus, when IL-1 was compared before treatment and 10 days after treatment, it was found that the indicators in both groups approached the limit in healthy groups and developed in positive dynamics. However, compared to the comparison group, it decreased in the main group (5.4±0.1 pg/ml) and almost reached the parameter in healthy individuals (3.35±0.4 pg/ml). However, the parameter in the comparison group was statistically significantly higher than in healthy individuals ($p<0.001$). In the main group, the IL-6 limit (5.8±0.2 pg/ml) changed more actively towards healthy individuals (3.27±0.3

pg/ml) compared to the comparison group (9.5±0.4 pg/ml). The decrease in TNF-α limit was more pronounced in the main group (5.3±0.2 pg/ml) than in the comparison group (9.4±0.4 pg/ml) reaching healthy individuals (4.2±0.3 pg /ml).

The positive effect of Immunofan was very pronounced in the main group, especially in the change in the concentration of immunoglobulins. Thus, the IgA limit was 1.9±0.03 in the main group and almost reached the value in the group of healthy individuals (1.6±0.2). On the 10th day of treatment, the limit of this parameter was 3.2±0.1 in the comparison group.

The level of IgG increased and changed more intensively in the main group (6.6±0.2) towards the healthy group (11.5±0.7). In the comparison group (6.9±0.4), this parameter was statistically significantly lower than the parameters of healthy individuals ($p<0.001$). After 10 days of treatment, the decrease in IgM limit level was more intensive than in healthy persons. It decreased in the main group (1.05±0.02) compared to healthy individuals (1.08±1.0), although it was not statistically significant. However, in the comparison group (1.32±0.08), it was slightly higher than that of healthy individuals.

When there is a chronic or acute infection foci in the body, the characteristics of immunocompetent cells and the immunological molecules contained in them can differ significantly from the characteristics of the same type of cells and molecules circulating in the blood. The study of the processes occurring in the area of surgical intervention, along with the study of general immune parameters, will make it possible to uncover the mechanisms of action in more detail, identify possible violations in time and carry out their correction.

Immune markers are of great importance in the determination of immunoglobulins in the blood for the prediction of calculous cholecystitis and provide a comprehensive profile of the body's immune response.

CONCLUSIONS

1. In 104 patients with destructive cholecystitis included in the study, biochemical indicators, cytokine profile and immunoglobulins were checked before surgery. The laboratory examinations of all patients revealed significant changes in CRP, IL-1, IL-6, TNF-α, and IgA, while there were no significant changes in ALT, AST, GGT indicators. While the CRP index was high in 86 out of 104 patients, the changes towards the increase in IL-1, IL-6, TNF-α, and IgA indicators in those patients attracted attention. However, although the CRP changed greatly in 18 patients, it was found that indicators such as IL-1, IL-6, TNF-α, and IgA did not reach limits. In this regard, patients were divided into two groups. Thus, 86 patients included in the main group were assumed to have a CRP limit higher than 17 mg/l, and IL-1, IL-6, TNF-α, and IgA limits higher than 13 pg/ml, and these patients received complex treatment in the postoperative period. It was considered necessary to use the immunomodulating drug Immunofan. In the other comparison group, 18 patients were assumed to have a CRP limit of 12-17 mg/l, IL-1, IL-6, TNF-α, and IgA limit of 12 pg/ml, and these patients were treated with conventional conservative treatment in the postoperative period [3,14,15].
2. Biochemical laboratory analysis indicators of blood samples obtained 10 days after surgery in patients with destructive cholecystitis in the comparison group were as follows: ALT - 25.4 V/l (60.5%), AST - 22.6 V/l (60.5%), GGT - 22.7 IU/l (36.8%), while CRP-8 mg/l (35%). Whereas in the main group the values of these parameters were for ALT-23.8 V/l (62.5%) ($t=1.09$, $p>0.05$), AST – 20.4 V/l (63.9%) ($t=1.03$, $p>0.05$), GGT – 19.4 IU/l (42.1%) ($t=1.03$, $p>0.05$), and CRP was –4.2 mg/l (81.8%) ($t=7.60$, $p<0.001$). The improvement in dynamics compared to the comparison group was recorded for ALT – 2%, AST – 2.4%, GGT – 5.3%, CRP – 46.8% in the main group [6, 8, 9, 14].

3. While cytokine profile indicators in blood samples obtained 10 days after surgery in patients with destructive cholecystitis in the comparison group were IL-1 – 8.5 pg/ml (21.2%), IL-6 – 9.5 pg/ml (22.2 %), TNF-α – 9.4 pg/ml (49.8%), in the main group these parameters were IL-1 – 5.4 pg/ml (60.9%) ($t=7.75$, $p< 0.001$), IL-6 – 5.8 pg/ml (62.6%) ($t=8.22$, $p<0.001$), and TNF-α – 5.3 pg/ml (68.3%) ($t=8, 20$, $p<0.001$). The dynamics of improvement were recorded in the main group compared to the comparison group: IL-1 – 39.7%, IL-6 – 40.4%, TNF-α – 18,5 % [13, 15].
4. In patients with destructive cholecystitis, in the blood samples obtained 10 days after the operation, the immunoglobulin analysis indicator IgA was 3.2 g/l (46%) in the comparison group, while in the main group - IgA - 1.9 g/l (85.4%) ($t= 13.0$, $p<0.001$). A 10% improvement in IgA-39.4% dynamics was recorded in the main group compared to the control group [12, 16].

PRACTICAL RECOMMENDATIONS

1. The importance of using immunomodulators in complex treatment after surgery was confirmed by studying cytokine status in patients with destructive cholecystitis along with diagnostic measures.
2. In order to improve the outcomes of patients with destructive cholecystitis, it is recommended to use the Imunofan drug in complex treatment after surgery.

LIST OF PUBLICATIONS ON THE TOPIC OF THE DISSERTATION

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4. R.B. Abbasaliev, M.Y. Nasirov, P.M. Abbasaliyeva The role and possibilities of immunofan in purulent - destruktive inflammation of the gallbladder during acute calculous cholecystitis in the perioperative period // Absracts of the XVIII international Euroasian congress of surgery and hepatogastroenterology. – Baku, – 11-14 september 2019, – p.198-199.
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7. R.B. Abbasəliyev Destruktiv xolesistitli pasiyentlərin qan nümunələrində interleykin fraksiyalarının miqdarına

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ABBREVİATİONS

ALP – alkaline phosphatase
ALT – alanine aminotransferase
AST – aspartate aminotransferase
CB – conjugated bilirubin
CRP – C-reactive protein
IgA – immunoglobulin A
IgG – immunoglobulin G
IgM – immunoglobulin M
IL-1 – interleukin 1
IL-10 – interleukin 10
IL-4 – interleukin 4
IL-6 – interleukin 6
GGT –Gamma-glutamyl transferase
UB –unconjugated bilirubin
TNF-α – tumor necrosis factor
ÜB –total bilirubin

The defense of the dissertation will be held at the ED 2.06 Dissertation Council meeting on "23" december 2024 at "16".

Address: 14 A. Gasimzade St., (conference hall), AZ 1022, Baku city.

The dissertation is accessible at the library of the Azerbaijan Medical University

Electronic versions of the dissertation and abstract are available on the official website of the Azerbaijan Medical University (amu.edu.az).

The abstract was sent to the required addresses on "16" november 2024.

Signed for print: 06.11.2024
Paper format: 60x84 1/16
Volume: 38652 characters
Order: 190
Number of hard copies: 30
“Tabib” publishing house