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THE ROLE AND POSSIBILITIES OF IMMUNOFAN IN PURULENT-DESTRUCTIVE INFLAMMATION OF THE GALLBLADDER IN ACUTE CALCULOUS CHOLECYSTITIS IN THE PERIOPERATIVE PERIOD

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Abstract

Timely urgent cholecystectomy in patients with ACC and ADCC, taking into account the possibility of using minimally invasive techniques using Immunofan, strengthens the immune system and significantly improves the results of surgical treatment. In the period from 2017 to 2018, 56 patients with various forms of acute calculous cholecystitis aged 15 to 86 years were hospitalized at the surgical clinic of the Azerbaijan Medical University. All 56 patients were divided into two groups: IA In the control group I entered 10 patients. II-In the main group, patients were divided into several subgroups. In subgroup A, 9 patients were operated on an emergency basis, for 5-6 hours with a diagnosis of destructive cholecystitis diffuse peritonitis. In subgroup B - 17 patients, after traditional preoperative preparation, with the addition of immunotherapy (immunofan), patients were operated on in an emergency order, within 12-48 hours. In the S-21 patients, perioperative therapy was carried out using immunotherapy (immunofan). All patients were examined according to the standard scheme: clinical examination, instrumental studies, laboratory tests.

Keywords
Immunofan, immunotherapy, acute calculous cholecystitis, acute destructive calculous cholecystitis, minimally invasive methods

Ота кезіндегі жіті калькулезді холецистит ауруына шалдыққанда өт қабының іріңді-деструктивтік қабынуы кезіндегі иммунофанның рөлі мен мүмкіндіктері

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Аңдатпа

Иммунофанды қолдануымен азинвазивті әдістерді пайдалану мүмкіндіктерін есепке алуымен жіті калькулезді холецистит (ЖКХ) мен жіті деструктивтік калькулезді холецистит (ЖДКХ) ауруларына шалдыққан ауруларды дер кезінде жедел холецистэктомия отасын жасау, иммунитетін күшейтеді және де хирургиялық емдеудің нәтижелерін айтарлықтай жақсартады. 2017 жылдан бастап 2018 жылға дейінгі мерзімінде Әзірбайжан медицина университетіне жас мөлшерлері 15 жастан 86 жасқа дейін жіті калькулезді холецистит ауруының түрлі нысандарымен 46 пациент ауруханаға жатқызылды. Барлық 46 пациент екі топқа бөлінде: I-А бақылау тобына 10 пациент кірді. II-В негізгі тобындағы аурулар бірнеше қосалқы топтарына бөлінді. А қосалқы тобындағы 8 ауруға жедел түрде ота жасалды, «деструктивтік холецистит диффузды перитонит» деген диагнозымен 5-6 сағат ішінде шұғыл түрде ота жасалған. Б қосалқы тобында дәстүрлі отаға дейінгі дайындықтан кейін – 12 ауруға, иммунотерапия (иммунофан) арқылы қосымша толықтыруымен пациенттеге жедел түрде 12-48 сағаттай ота жасалды. С қосалқы тобының -16 - ауруына иммунотерапия (иммунофан) арқылы ем жасалған. Барлық пациенте стандарты сызба бойынша тексерілген: клиникалық қарап тексеру, құралдар арқылы тексеру, зертханалық зерттеулер.

Түйін сөздер
иммунофан, иммунотерапия, жіті калькулезді холецистит (ЖКХ), жіті деструктивтік калькулезді холецистит (ЖДКХ), азинвазивті әдістер.

Роль и возможности иммунофана в гнойно-деструктивном воспалении желчного пузыря при остром калькулезном холецистите в периоперационном периоде

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Аннотация

Своевременная срочная холецистэктомия у больных с ОКХ и ОДКХ с учетом возможности применения малоинвазивных методик с применением Иммунофана усиливает иммунитет и заметно улучшает результаты хирургического лечения. В период с 2017 по 2018 годы в хирургическую клинику Азербайджанского медицинского университета были госпитализированы 56 больных с различными формами острого калькулезного холецистита в возрасте от 15 до 86 лет. Все 56 пациентов были разделены на две группы: I-А в контрольную группу я вошли 10 пациентов. II-В основной группе, больные были подразделены на несколько подгрупп. В подгруппе А 9 больных были оперированы в экстренном порядке, в течение 5-6 часов с диагнозом деструктивный холецистит диффузный перитонит.В подгруппе Б- 17 больных, после традиционной предоперационной подготовки, с дополнением иммунотерапии(иммунофана), пациенты были оперированы в экстренном порядке, в течение12-48часов. В подгруппе С-21-больным проводили в периоперационном периоде терапию с использованием иммунотерапии (иммунофана). Все пациенты были обследованы по стандартной схеме: клинический осмотр, инструментальные исследования, лабораторные исследования.

Ключевые слова
Иммунофан, иммунотерапия, Острый калькулезный холецистит, острый деструктивный калькулезный холецистит малоинвазивные методы

The relevance of the problem. Currently, acute cholecystitis is one of the most common urgent diseases in surgery. One of the controversial issues is the question of rational surgical tactics, the choice of the timing of the operation in acute cholecystitis. Despite a significant improvement in the results of treatment, the mortality after urgent operations for acute cholecystitis remains several times higher than with planned and delayed surgical interventions, varies in different institutions within 2-12%, has no tendency to decrease and reaches during operations on the height of the attack 14-15%, and in the elderly patients - 20%, increasing sharply with age. During urgent operations in patients older than 80 years, postoperative mortality exceeds 40-50%, which makes these operations extremely risky. At the same time, planned and delayed operations performed on the background of the calmed down acute inflammatory process, after a comprehensive examination and preparation of the patients, give significantly better results. Postoperative mortality in such cases reaches in individual surgeons 0.5–1% [Borodach V.A. et al., 2005].

Most surgeons are now in favor of active surgical tactics, which is based on the desire to remove the purulent-inflammatory focus in the early stages after hospitalization of patients (within 24-72 hours) and thus prevent the development of dangerous complications - perforation of the gallbladder wall, peritonitis, cholangitis, migration of concrements to choledoch [Yermolov AC 2004, Lubsky A.C., 2005; Alobaidi M. et al., 2005].

Surgeons who prone to conservative and expectant tactics, as the main argument put forward data on significantly lower mortality after operations performed in the “cold” period, compared with urgent operations [Kuliev Sh.B., Isaev G.B., 1990]. According to M.M. Tagiyev (1988) mortality with delayed operations was 3 times lower,

Some authors emphasize the importance of using antibiotics to relieve an attack [Malyuga V.Yu., 2000; Tambyraja AL. et al., 2004]. But there is another opinion: none of the antibiotic administration regime before surgery does not completely eliminate the infection, even if an active against bile microflora drug is used.

Materials and research methods. In the period from 2017 to 2018, 56 patients with various forms of acute calculous cholecystitis aged from 15 to 86 years were hospitalized at the surgical clinic of the Azerbaijan Medical University. All 46 patients were divided into two groups:

I - in the control group entered 10 patients. II - in the main group, patients were divided into several subgroups.

In subgroup A - 9 patients were urgently operated, for 5-6 hours with a diagnosis of destructive cholecystitis, diffuse peritonitis.

In subgroup B - 16 patients, after the traditional preoperative preparation, with the addition of immunotherapy (immunofan), the patients were operated urgently within 12-48 hours

In subgroup C - 21 patients, perioperative therapy was carried out providing immunotherapy

(immunofan). All patients were examined according to the standard scheme: clinical examination, instrumental examinations (R-scopy of the chest, ultrasound diagnostics of abdominal organs, electrocardiography, external respiration function), laboratory tests (complete blood and urine analysis, biochemical blood test: bilirubin level, ALaT, ASaT, glucose, total protein.

Duration of the disease varied from 5 hours to 7 or more days. Of all patients with acute calculous cholecystitis, 9 (16.1%) were hospitalized up to 6 hours from the onset of the disease. In 16 (28.6%) patients, the duration of the disease was 6-24 hours, and 21 (37.5%) patients were admitted to the surgical department after 24 hours from the onset of acute destructive cholecystitis.

37 (66.1) patients in the main subgroups A and B with ACCh and ADCCh in the preoperative and postoperative period were given immunofan according to our methodology, and 10 (17.9) patients in the control group were treated with the traditional method. Blood of the patients was studied: in the preoperative, postoperative period and before the discharging. The following immunological parameters were studied: the absolute content of blood leukocytes, the relative and absolute blood levels of the lymphocytes and their subpopulations: T-lymphocytes, T-helper cells, T-cytotoxic cells, MDS-cells, B-lymphocytes, activated T-lymphocytes, T-helper and T-cytotoxic cells ratio, absolute levels of immunoglobulins A, M, O, phagocytic activity of leukocytes (PAL), phagocytic index (PI), phagocytosis completion index (PCI), IgA - Immunoglobulin A, IgG - Immunoglobulin G, IgM - Immunoglobulin M, NBT test (spontaneous and stimulated), NBT load Index, circulating immune complexes (CIC), the relative and absolute blood levels of monocytes, eosinophils, stab and segmented leukocytes. These immunological indicators in the comparison groups before the operation are shown in table 1.

We analyzed in detail the immunological indicators in patients of the main and control groups before the operation, where: absolute leukocyte count, absolute and relative lymphocyte count, absolute monocyte, eosinophil, band and segmented leukocytes counts, absolute blood levels of T-lymphocytes, T-helpers, B-lymphocytes and phagocytosis completeness index differed significantly.

Table 2 shows the ratio of the absolute levels of leukocytes among patients (ACCh) and (ADCCh). As can be seen from table 2, the average level of blood leukocytes before the operation in ACCh is significantly and reliably lower than in ADCCh ($p < 0.05$).

In the majority of patients with the ACCh-control group, the level of blood leukocytes varied within the normal range, while in all patients with ADCCh, the level of leukocytes was elevated.

Taking into account the data in Table 2, it can be assumed that the level of blood leukocytes in patients in the control group with ACCh is an additional criterion for the risk of the development of ADCCh. I.e. if patients with acute cholecystitis have an increased level of blood leukocytes, there is a risk of developing an acute form of destructive cholecystitis in these patients. In patients with a usual ACCh course, (the control group) blood lymphocytes (absolute and relative) were at the upper limits of the norm or elevated, which corresponds to modern ideas about the response of the immune system to the inflammatory process in the body, because the normally functioning immune system responds with lymphocytosis on acute destructive inflammation in the body, which we observed in patients with ADCCh. And the presence of a reduced level of absolute and relative content of lymphocytes in the main group confirms the assumption that patients with ACCh have a weakened reaction (lymphocytopenia) of the immune system to destructive inflammation.

Table 1.
Immunological indicators in the comparison groups

Immunological indicators (Normal value)	Groups of patients	
	ACCh control group (n=10)	ADCCh + Immunofan (n=37)
Leukocytes (4600-7100 cells/μl)	6200±1170	9578±1471
Lymphocytes (1600-2400 cells/μl)	1058±44,7	1599±79,4
T-lymphocytes (1100-1900 cells/μl)	Г114±57,6	970,3±42,8
B-lymphocytes (200-600 cells/μl)	1’73,6±120,6	164,4±82,49
Monocytes (450-600 cells/μl)	400,2±28,4	579,9±37,4
Eosinophils (120-180 cells/μl)	108,9±6,7	142,29±15,09
Band cells (500-1100 cells/μl)	469±24	901±51,4
Segmented cells (5000-6000 cells/μl)	3805±109	5462±155,5
ESR (2-25 mm/h)	18,95±6,7	19,7±4,9
T-helpers (700-1400 cells/μl)	609,2± 30,8	956,3±56,3

Table 2.
Description in the text

Indicators	Groups of patients	
	ACCh control group (n=10)	ADCCh + Immunofan (n=47)
Leukocytes (cells/μl)	6377±1226	9578±1571

In this regard, in the preoperative period, we prescribe Immunofan according to our method, which enhances the weakened response of the immune system to the flowing purulent-destructive inflammation in the body.

Considering that patients in the main group have a significantly lower level of absolute and relative blood lymphocyte count before surgery, due to the effect of Immunofan, than in control group, when studying lymphocyte subclasses, we also found lower T- and B- lymphocyte counts in blood of the patients with acute destructive cholecystitis. The T-lymphocyte counts in the comparison groups before the operation in patients with the ACCh-control group showed that the absolute content of T-lymphocytes in the blood before the operation was below the norm, and in the main group the absolute content of T-lymphocytes in the blood was increased or at the upper limit of the norm. Since T-lymphocytes perform very important functions in the body: effector and regulatory, their lack in blood can lead to a decrease in the specific cytotoxicity of T-lymphocytes and dysregulation of B-lymphocyte activity, as well as neutrophils and macrophages that carry out phagocytosis of microorganisms. All of the above may be a prerequisite for defective functioning of the immune system: the disruption of T-lymphocytes and phagocytes may lead to the deposition of microorganisms in the focus of inflammation (gallbladder) and the relief of destructive inflammation.

Based on the data, it can be assumed that the presence of reduced absolute levels of blood T-lymphocytes in a patient with acute cholecystitis may increase the risk of developing ACCh, the appointment of an immunofan according to the proposed method can be used as a criterion (together with other indicators) in complex diagnostics and prediction of ACCh

The content of T-helpers in patients with ACCh-control group before the operation was reduced in a similar way, which indicates a weakened response of the immune system to destructive inflammation. The content of T-helpers in patients of the main group was within the normal range or moderately elevated, which corresponds to the ideas about the dynamics of the immune status during the developing inflammatory process in the body. The reduced content of T-helper cells in patients with ACCh is probably the result of a general decrease in blood lymphocytes in these patients. Such inhibition of the cellular element of the immune system may possibly affect the character of the clinical course of destructive inflammation in the body.3.3

Emergency surgery is indicated to patients with acute calculous cholecystitis with obvious clinical signs of obstruction and destruction, purulent intoxication, cholangitis and peritonitis in the shortest time since hospitalization after sufficient preoperative preparation. The diagnosis can be verified by ultrasound or laparoscopy according to indications. In the absence of indications for emergency surgery, treatment begins with a complex of conservative therapy. The diagnosis can be specified basing on the clinical data and the results of ultrasound. The clinical picture of acute calculous cholecystitis is characterized by the presence of a typical and pronounced pain attack, an increased painful gallbladder, local muscle tension, increased body temperature, leukocytosis, tachycardia, bile vomiting, dry and furrowed tongue, Ortner and Blumberg symptoms (in the presence of the latter, indicating the presence of peritonitis, which is an absolute indication for emergency operation). An enlarged, disconnected gallbladder with signs of inflammation or destruction of the wall, signs of stagnation in the cystic cavity are determined on ultrasonography. With an established diagnosis of acute obstructive cholecystitis, the effectiveness of conservative therapy is assessed within 24 to 48 hours (optimally within one working cycle, maximum 72 hours). In the absence of a clinical effect of conservative therapy, an urgent operation is indicated, ultrasound control is not required. IMUNNOFAN was being prescribed to patients in the preoperative and postoperative periods. The effect of the drug begins to develop within 2-3 hours after administration and lasts up to 4 months. The drug does not significantly affect the production of reagin antibodies of the IgE (Immunoglobulin E) and does not enhance the

Table 3.
Description in the text

Indicator (Normal value)	Patients group	
	ACCh – control group (n=10)	ADCCh + Immunofan (n=37)
T-helpers (700-1400 (cells/μl)	609,2± 30,8	956,3±56,3
p<0,05*		

immediate-type hypersensitivity reaction. The drug stimulates the formation of IgA (immunoglobulin A) in its congenital insufficiency. Immunofan effectively suppresses the multidrug resistance of tumor. Immunological research was conducted on the basis of the clinic of the Azerbaijan Medical University. On the basis of the obligatory ultrasound control, which allows diagnosing and operating patients with ACCh urgently, it has become possible to reduce the amount of perivesial complications during delayed operations from 37% to 9%. The tactics justified in this way became the standard for treating patients with acute calculous cholecystitis (ACCh) in our clinic. In the course of work, in the process of establishing a number of clinical signs characteristic for ACCh, new data was being taken into account when choosing surgical tactics. Practical development of the diagnostic criterias allowed us to practically avoid the occurrence of the ADCCh in delayed operations. In our observations, postoperative complications occurred in 3 out of 47 patients (6.4%) and were significantly lower ($p > 0.05$) than in patients in the ADCCh group - 28.2%. All cases of postoperative complications in patients with ACCh were of a different nature. In 1 case, wound suppuration was noted after open cholecystectomy. In 1 case right-sided pneumonia occurred after open surgery. Thus, taking into account the possibility of using minimally invasive techniques, Immunofan therapy strengthens the immune system and markedly improves the results of surgical treatment after timely urgent cholecystectomy in patients with ACCh,. Considering the data of a comparative analysis of indicators; immunity of patients with ACCh and with the usual course of destructive cholecystitis, the following conclusions can be drawn:

This suggests that the immune system of the surveyed patients with ADCCh retains the ability to perform its function, but apparently, it works defectively in one or several links. Other authors also obtained similar results of researches on the content of immunoglobulins in patients with ACCh. Identification of distinctive clinical and immunological signs made it possible to distinguish among all patients with acute cholecystitis a group of patients with acute destructive calculous cholecystitis.

Patients with ADCCh prevailed among patients under 60 years of age, with recurrent seizures; these patients had a high level of extra-abdominal postoperative complications (4 times higher than in patients in the control group).

In the group of patients with ADCCh, before surgery, significant suppression of the immune status was detected (by 13–34% of the norm), in particular, such indicators as T-lymphocytes, T-helpers. In the postoperative period, in patients with ADCCh, against the background of the combined therapy, normalization of T-lymphocyte levels was observed, however, the levels of T-helper cells, as well as the index of completion of phagocytosis, remained long-term reduced (by 8 - 19% of the norm). An integrated approach to the diagnosis of acute destructive calculous cholecystitis allowed to identify patients in need of urgent surgical intervention, with a simultaneous increase in the frequency of minimally invasive operations in this group of patients. In turn, this led to a decrease in the frequency of postoperative complications from 11.6% to 4.3%.

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