State of Immunity and Methods of Correction in Patients with Ventral Abdominal Hernia on the Background of Chronic Uro-Genital Infection

Isayev Hidayat, Aliyev Yusif and Isayeva Aynur
Scientific Surgery Centre Named after Acad. M. A. Topchubashov, Baku AZ1000, Azerbaijan

Abstract: The article considers resulting materials of examination and treatment of 88 patients (31 men, 57 women, the main group), aged 22-45 who applied to the Scientific Center of Surgery in order to have hernioplasty, in whom, chronic urogenital infections (CUGIs) were detected in various combinations viabacterioscopic, cultural and serological tests addressed to the research center of surgery for application of herniaplasty. Recurrent ventral hernia was diagnosed in 79 patients and umbilical hernia—in 9 patients. The control group consisted of 20 patients with hernias of the anterior abdominal wall, which did not have any chronic infections or concomitant diseases that negatively affect the parameters of immune system. The state of the cellular and humoral link of the immune system in patients with chronic urogenital infections was characterized by the presence of suppression in the T-cell link and an imbalance in the parameters of humoral immunity. The presence of clinical signs of immunodeficiency in patients with hernias of the anterior abdominal wall is a direct indication for the appointment of immune corrective therapy in the preoperative period. In patients with chronic urogenital infections, Likopid has a noticeable immune corrective effect, which is manifested in the form of positive dynamics of indicators of both cellular and humoral immunities; at the same time, Likopid therapy in combination with 0.33% saffron tincture is a more effective method of immune correction.

Key words: Ventral abdominal hernia, uro-genital infection, immuncorrection, saffron.

1. Introduction

Ventral abdominal hernia is one of the most common surgical diseases; only in Russia, according to the summary data of a number of authors, from 10 to 12 million people suffer from ventral hernias, which is a significant medical and social problem [1, 2].

Despite the introduction of modern inert plastic materials, tension-free plastic techniques, laparoscopic technologies for eliminating hernias, the frequency of postoperative complications is on average 5% [3, 4]. One of the causes of complications after hernia repair is a decrease in immune system response [5]. During the last decade, there has been an increase in chronic urogenital infections (CUGIs) [6, 7]. This leads to the frequent development of UGC among patients with abdominal hernias.

Corresponding author: Isayev Hidayat, Doctor Med. Sci., Professor, research field: general surgeon.

Literature data show the leading role of the immune system in the pathogenesis of urogenital infection. Many authors have found that the most significant changes in the cellular and humoral immune systems were found in patients with chlamydia infection [8, 9]. An even greater role belongs to the immune system during persistence of the pathogen, when a conditional balance is established between the microorganism and the macroorganism. CUGIs are accompanied by immune disorders in 82% of women and 80% of men [10, 11]. Impaired immunity contributes to a significant decrease in the regenerative abilities of connective tissue [12]. Surgery performed against this background is accompanied by multiple postoperative complications, including recurrent hernia and rejection of alloprostheses [13].

In the treatment of recurrent CUGIs, the effectiveness of therapy without the use of immune modulators rarely exceeds 50% [14, 15]. Currently, in
the treatment of diseases associated with chronic infections, various drugs are used that affect the immune system. It has now been established that the most effective stimulators of innate immunity are the bacterial cells themselves and (or) their structural components. DNA containing CpG sequences and muramyl peptides of the cell wall peptidoglycan has the greatest immune stimulating effect in the composition of a bacterial cell. These compounds are unique and are found only in prokaryote cells [16, 17]. On the basis of cell wall peptidoglycan, a whole generation of low molecular weight, synthetic or semi-synthetic bacterial immune stimulants have been created, which have received permission for medical use: Likopid® (Russia), Mifamurtid® (European Union) and Romurtid® (Japan). Ultimately, all of these drugs are derivatives of N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP).

Our attention was caught by Likopid® (Russia), which has a pronounced immunotropic effect, as well as saffron tincture.

Likopid® is administered orally on an empty stomach, 30 minutes before meals. The biological activity of the drug is realized through the binding of GMDP to the intracellular receptor protein NOD2, localized in the cytoplasm of phagocytes (neutrophils, macrophages, dendritic cells).

The drug stimulates the functional (bactericidal, cytotoxic) activity of phagocytes, enhances the presentation of antigens by them, the proliferation of T- and B-lymphocytes, increases the synthesis of specific antibodies, helps to normalize the balance of Th1/Th2 lymphocytes towards the prevalence of Th1. The pharmacological action is carried out by increasing the production of key interleukins (interleukin-1, interleukin-6, interleukin-12), TNF alpha, gamma-interferon, colony-stimulating factors. The drug increases the activity of natural killer cells. Likopid® has low toxicity (LD50 exceeds the therapeutic dose by 49,000 times or more). The oral bioavailability of the drug is 7-13%. The degree of binding to blood albumin is weak. The time it reaches Cmax is 1.5 hours after administration, T1/2—4.29 h. It does not form active metabolites and is excreted in unchanged state mainly through the kidneys [18].

Since ancient times, saffron has been widely used in folk medicine of the East: in the form of tea leaves, alcoholic tincture, it is used in patients with heart conditions, leukemia, eye diseases, as well as an analgesic, diuretic and antiseptic [19, 20]. In clinical practice, the use of saffron in patients with purulent-septic diseases significantly improved the parameters of humoral and cellular immune systems [21-23].

The objective is to propose an adequate method of immune correction in the preoperative period in patients with hernias of the abdominal wall with the background of chronic urogenital infections.

2. Methods

Taking into account the increase in the incidence of chlamydia among the population and its role in the development of relapses after previous hernia repair, we investigated the presence of any chronic urogenital infections in all patients admitted to surgical treatment for recurrent hernias. The materials underlying this work were obtained as a result of examination and treatment of 88 patients (31 men, 57 women, the main group), aged 22-45 who applied to the Scientific Center of Surgery in order to have hernioplasty, in whom, HUGIs were detected in various combinations viabacterioscopic, cultural and serological tests.

Recurrent ventral hernia was diagnosed in 79 patients and umbilical hernia—in 9 patients. The control group consisted of 20 patients with hernias of the anterior abdominal wall, which did not have any chronic infections or concomitant diseases that negatively affect the parameters of immune system.

The main signs of chronic urogenital infections (CD3+ T-lymphocytes) were: general weakness and malaise (84% of cases), joint pain (21%), various skin rashes (19%), a tendency to allergies (38%), itching in
the genitals (85%) and a burning sensation in the genitals after coitus (42% of cases). On the basis of these complaints, laboratory methods should be used to confirm or exclude the presence of HUGIs. Within the generally accepted regulations bacterioscopic, cultural research methods, polymerase chain reaction (PCR), immunoenzymatic (IFA) analysis and serological diagnostic methods (microprecipitation, Wasserman reaction, and passive hemaglutination reaction) were performed in order to detect the urogenital infections.

Well-known indicators of cellular and humoral immune systems (Ig M, G and A) and the extent of phagocytosis were determined in order to identify the state of the immune system. The amount of immune component cells that had receptors of various phenotypes located on their surface was calculated.

In an objective study, 35 (61.4%) women out of 57 revealed inflammatory changes in their vaginal mucosa; of these, 18 (51.4%) patients had an inflammatory discharge. And 19 (33.3%) women had cervical erosions of various degrees. In the total analysis of blood on the HUGI background, the number of lymphocytes was 10% lower in men and 12.5% lower in women compared to the control group. In the control group, the number of monocytes was higher by 72% in women and by 124% in men compared to the main group. In the main group, the number of eosinophils in peripheral blood was higher by 88% in men and by 88.7% in women compared to the blood count analysis of the control group. General analysis of urine in 18 patients (5 men and 13 women) of the main group revealed the presence of HUGIs.

Bacteriological tests, PCR, IFA and serological analyses in the main group of patients revealed HUGIs in various combinations (chlamydia + trichomonas in 24 patients, chlamydia + ureaplasma + mycoplasma in 42, chlamydia + ureaplasma + mycoplasma in 42 and chlamydia + ureaplasma in 22 patients).

We divided the main group into two subgroups (A and B), 44 patients each. In subgroup A, the immune correction was carried out with Likopid, and in subgroup B Likopid was used in combination with saffron tincture. Likopid was prescribed as 1 tab (10 mg)/day daily, before meals, for 14 days to the patients of both subgroups and in subgroup B, in addition to Likopid, 100 mL of 0.33% saffron tincture was added to the food intake. On the 14th day, immunological studies were carried out in both subgroups and the obtained results were compared between the subgroups and then with the results of the original studies and with the control group results.

3. Results and Discussions

The study of parameters of the cellular and humoral links of the immune system was carried out in patients of both groups. The obtained results are shown in Table 1.

As can be seen from the table, the patients of the main group were initially found to have multifactorial disorders in the cellular link of immune system. Thus, in the main group, compared to the control group, there is a significant decrease in the total number of lymphocytes ($p < 0.05$), CD3 + T-lymphocytes, CD3+/CD4 + lymphocytes ($p < 0.05$; $p < 0.01$), IRI indicators (CD4+/CD8 +) ($p < 0.05$; $p < 0.001$), CD3—HLA-DR + cells ($p < 0.01$) and activated CD3 + HLA-DR + T lymphocytes ($p < 0.001$). In addition, there was an increase in the content of CD3+/CD8 + -T-cytotoxic lymphocytes, up to one hundred ($p < 0.001$) increase in the level of CD19 + B-lymphocytes, CD3-CD16 + CD56 + -EKK ($p < 0.01$; $p < 0.001$) and CD3 + CD16 + CD56 + -T-killers. Disturbances in the humoral link of the immune system were characterized by a decrease in the content of IgG ($p < 0.05$; $p < 0.01$) and IgA ($p < 0.001$) with a slight increase in the IgM levels.

The revealed changes in the cellular and humoral links of the immune system in patients with chronic chlamydia indicate suppression of the T-cell link, due to a significant ($p < 0.05$) decrease in the total number of lymphocytes, CD3+ T-lymphocytes, IRI...
The dynamics of the 14th day, a positive trend was noted in the presence of suppression in the T cell link and an imbalance of humoral immune system. We considered the presence of clinical signs of immunodeficiency in patients with hernias of the anterior abdominal wall as a direct indication for prescribing immune corrective therapy in the preoperative period.

As the results of immunological studies, reflected in the table show, on the 14th day, a positive trend was noted in the form of an increase in the parameters of cellular immunity in patients who received Likopid (subgroup A): for example, if the number of lymphocytes reached 32.2 ± 1.1% in 44 patients with hernias of the abdominal wall with the background of CUGIs, then after immune correction with immunofan it increased up to 35.7 ± 1.2%, or by 10.8%. However, in subgroup B (Likopid + saffron tincture), the number of lymphocytes on the 14th day reached 36.1 ± 1.2% (increase by 12.7%), almost coinciding with the indicator of the control group (36.2 ± 1.4%).

The number of T-lymphocytes (CD3 +) in subgroup A increased by 28.1%, in subgroup B—by 29.3%. The quantity of T-helpers (CD3 +/CD4+) underwent an almost identical change. In the dynamics of T-cytotoxic lymphocytes (CB3 +/CB8 +), a similar pattern was also observed: their share in the

| Indicators                                      | Control group (n = 20) | Initially   | 14th day after immune correction |
|------------------------------------------------|------------------------|-------------|---------------------------------|
| Lymphocytes, %                                 | 36.2 ± 1.4             | 32.2 ± 1.1* | 35.7 ± 1.2*                     |
| T-lymphocytes (CD3+), %                        | 68.5 ± 1.3             | 52.9 ± 1.4**| 67.8 ± 1.3*                     |
| T-helpers (CD3+/CD4+), %                       | 41.3 ± 1.4             | 35.7 ± 1.2* | 40.8 ± 0.9*                     |
| Cytotoxic T cells (CD3+/CD8+), %               | 24.3 ± 0.8             | 26.2 ± 1.3* | 25.5 ± 1.3*                     |
| Immune regulatory index (IRI) (CD4+/CD8+)      | 1.97 ± 0.06            | 1.72±0.09*  | 1.91 ± 0.07**                   |
| B-lymphocytes (CD19+), %                       | 14.6 ± 0.5             | 25.8 ± 1.7* | 16.3 ± 1.2*                     |
| Natural killer cells (NKC) (CD3-CD16+CD56+), %| 18.7 ± 0.6             | 23.1 ± 1.3* | 19.2 ± 0.9**                    |
| T-killer cells (CD3+CD16+CD56+), %            | 3.4 ± 1.1              | 5.2 ± 0.9*  | 3.6 ± 0.7*                      |
| CD3-HLA-DR+ cells, %                           | 16.5 ± 1.3             | 13.9 ± 1.2* | 16.1 ± 1.0*                     |
| Activated T lymphocytes (CD3+HLA-DR+), %       | 11.6 ± 0.5             | 8.2 ± 0.7*  | 10.7 ± 0.8*                     |
| IgA, g/L                                       | 2.47 ± 0.08            | 1.76 ± 0.15**| 2.4 ± 0.17**                   |
| IgM, g/L                                       | 1.83 ± 0.16            | 2.34 ± 0.48**| 1.96 ± 0.24**                  |
| IgG, g/L                                       | 12.92 ± 0.54           | 10.7 ± 0.6* | 12.6 ± 0.42*                   |

(Note: * p <0.05; ** p <0.01 - significant differences from the control group)

(CD4 +/CD8 +) and activated CD3 + HLA-DR + T lymphocytes. The detected increase in the level of CD19 + -B-lymphocytes, CD3 + CD16 + CD56 + T-killers and CD3-CD16 + CD56 + -EKK, apparently, is due to the adaptive mechanisms of the immune system aimed at eliminating the infectious agents. The evident decrease in the secretion of IgA and IgG is a consequence of an imbalance in the cellular link of the immune system, due to the suppression of the activity of both cellular and humoral immune systems, and these changes concerned almost all studied parameters. The most significant decrease was in the content of the total number of lymphocytes, T-lymphocytes and IRI. Indicators of the total number of lymphocytes, CD3 +/CD4 + lymphocytes, IRI, CD3 + CD16 + CD56 + lymphocytes and CD3-HLA-DR + -cells did not have significant differences with the control group. These changes indicate the suppression of the specificity of the immune response in patients with chronic chlamydia infection. Thus, the indicators of the cellular and humoral links of the immune system in patients with HUGIs were characterized by the presence of suppression in the T-cell link and an imbalance of humoral immune system. We considered the presence of clinical signs of immunodeficiency in patients with hernias of the anterior abdominal wall as a direct indication for prescribing immune corrective therapy in the preoperative period.

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lymphocyte subpopulation after immune correction with imunofan decreased by 2.7%, and after the use of imunofan in combinations with saffron tincture—by 7.6%. In patients of the main group, the percentage of B-lymphocytes at the initial examination exceeded the indicators of patients in the control group by 43.4%, after immune correction for 14 days in subgroup A (Likopid)—by 11.6%, and in subgroup B (Likopid + saffron)—only by 0.7%.

As can be seen from the table, the level of circulating complexes in subgroup A on the 14th day exceeded the initial one by 11%, in subgroup B—by 13.4%; positive dynamics of other indicators of cellular immunity (NKK, T-killers, CD3—HLA-DR + cells, activated T-lymphocytes) were also noted as a result of the immune therapy. However, in subgroup B these positive changes exceeded those in subgroup A by an average of 10-20% (p < 0.05). More significant positive dynamics were noted in both subgroups on the 14th day in the study of the humoral link of immune system (IgG, IgM and IgA) too. However, in subgroup B, the improvements were 9-40% more pronounced than in subgroup A (p < 0.05).

4. Conclusions

(1) The presence of chronic urogenital infections in patients with hernias of the abdominal wall contributes significantly to the cause of various complications after hernia repair.

(2) The state of the cellular and humoral link of the immune system in patients with chronic urogenital infections was characterized by the presence of suppression in the T-cell link and an imbalance in the parameters of humoral immunity.

(3) The presence of clinical signs of immunodeficiency in patients with hernias of the anterior abdominal wall is a direct indication for the appointment of immune corrective therapy in the preoperative period.

(4) In patients with chronic urogenital infections, Likopid has a noticeable immune corrective effect, which is manifested in the form of positive dynamics of indicators of both cellular and humoralimmunities; at the same time, Likopid therapy in combination with 0.33% saffron tincture is a more effective method of immune correction.

References

[1] Sukovatykh, B. S., Valuyksaya, N. M., Gerasimchuk, E. V., Pravednikova, N. V., and Mutova, T. V. 2014. “Efficiency of Mini-abdominoplasty in the Treatment of Large Ventral Hernias.” *Annaly khirurgii* 5: 37-43. (in Russ.)

[2] Sukovatik, B. S., Blinkov Y. Y., Netyaga, A. A., Zatolokina, M. A., Polevoy, Y. Y., and Zhukovskiy, V. A. 2020. “Effectiveness of Light Strengthened Endoprosthesis in the Treatment of Middle and Large Ventral Hernia.” *Khirurgiiia* (7): 39-44. doi: 10.17116/khirurgia202007139.

[3] Ermolov, A. S., Blagovestnov, D. A., Alekseev, A. K., Upyrev, A. V., Yartsev, P. A., Shlyakhovskiy, I. A., Koroshvili, V. T., and Burbu, A. V. 2019. “Optimized Approach to the Surgical Treatment of Patients with Large and Giant Postoperative Ventral Hernia.” *Khirurgiiia (Mosk)* (9): 38-43. doi: 10.17116/Chirurgia201909138.

[4] Den Hartog, D., Dur, A. H., and Kamphuis, A. G. 2009. “Comparison of Ultrasonography with Computed Tomography in the Diagnosis of Incisional Hernias.” *Hernia* 13 (1): 45-48.

[5] Evans, K. K., Chim, H., Patel, K. M., et al. 2012. “Survey on Ventral Hernias: Surgeon Indications, Contraindications, and Management of Large Ventral Hernias.” *Am. J. Surg.* 78 (4): 388-97.

[6] Kubanova, A. A., Kabanov, A. A., and Melekhina, L. E. 2018. “Dynamics of Incidence of Sexually Transmitted Infections in the Evaluation of the Epidemiological Process and State of Health of the Russian Federation Population in 2006-2016.” *Vestnik Dermatologii i venerologii* 41 (4): 27-37.

[7] Wagenlehner, F. M. E., Brockmeyer, N. H., Discher, T., Friese, K., Wichelhaus, T. A. 2016. “The Presentation, Diagnosis, and Treatment of Sexually Transmitted Infections.” *Dtsch Arztebl Int.* 113 (1-2): 2016. doi: 10.3238/arztebl.2016.0011.

[8] Boldyreva, M. N., Lipova, E. V., and Vitvitskaya, Y. G. 2010. “Sexually Transmitted Diseases in Women. Caused by Opportunistic Microflora: How to Identify and Correction.” *Vestnik dermatologii i venerologii* 2: 26-31. (in Russian)

[9] Gomberg, M. A., Chernousov, A. D., and Soloviov, A. M.
2001. “Immunotherapy in the Management of Chlamydia Trachomatis Infection.” Int. J. STD AIDS 12 (Suppl. 2): 10.

[10] Workowski, K. A., and Bolan, G. A. 2015. Sexually Transmitted Diseases Treatment Guidelines. MMWR Recomm Rep 2015, 64 (RR-3).

[11] Rowley, J., Vander Hoorn, S., Korenromp, E., et al. 2019. “Chlamydia, Gonorrhoea, Trichomoniasis and Syphilis: Global Prevalence and Incidence Estimates, 2016.” Bull World Health Organ 97 (8): 548-62. doi: 10.2471/BLT.18.228486.

[12] Su, H., and Caldwell, H. D. 1995. “CD4+ T-cells Play a Significant Role in Adoptive Immunity to Chlamydia Trachomatis Infection of the Mouse Genital Tract.” Infect. Immun. 63 (9): 3302-8.

[13] Aleshkin, V. A., Makarov, O. V., and Shaykov, K. A. 2000. “Status of Local Immunity in Inflammatory Diseases of the Female Genital Tract and the Impact It Immunomodulatory Kipferon Modulator.” Imunnopatologiyai klinicheskaya immunologiya 5: 41-4. (in Russian)

[14] Fedoseyev, A. V., Rybachkov, V. V., Trushin, S. N., Lebedev, S., and Ninyutin, A. S. 2019. “Preventive Abdominal Wall Repair in High-Risk Groups of Postoperative Ventral Hernia.” J. Chirurgiya (1): 32-6. (in Russian).

[15] Braam, J. F., Van Dommelen, L., Henquert, C. J. M., Van De Boven-Kamp, J. H. V., and Kusters J. G. 2017. “Multidrug-Resistant Mycoplasma Genitalium-Fections in Europe.” Eur J Clin Microbiol Infect Dis. 36: 1565-7.

[16] Sailer, F., Rait, G., Howe, A., Saunders, J., and Hunter, R. 2018. “Methods and Quality of Disease Models Incorporating More Than Two Sexually Transmitted Infections: A Protocol for a Systematic Review of the Evidence.” BMJ Open 8 (5): e020246. doi: 10.1136/bmjopen-2017-020246.

[17] Pinegin, B. V., and Pashchenkov, M. V. 2019. “Immunostimulators of Muramylpeptide Nature in the Treatment and Prevention of Infectiousinflammatory Processes.” Иммунология 40 (3): 65-71.

[18] Ivanov, V. T., Khaitov, R. M., Andronova, T. M., and Pinegin, B. V. 1996. “Likopid (glucosaminilmuramilpentapeptide)—New Domestic Highly Effective Immunomodulator for Treatment and Prophylaxis of Diseases Associated with Secondary Immunological Insufficiency.” Immunologiya 17 (2): 4-6. (in Russian)

[19] Pinegin, B. V., Andronova, T. M., and Karsonova, M. I. 2005. “Muramylpeptide Preparations—Immunotropic Drugs of New Generation.” In Likopid in the Complex Treatment and Prevention of Immunodeficiency States. Moscow, 19-36. (in Russian)

[20] Sokolov, S. Y. 2000. Herbal Medicine and Pharmacology: A Guide for Physicians. Moscow: MIA.

[21] Malakhova, R. S. 2002. Medicinal Plants: A Handbook. Moscow: RIPOLKLASSIK. (in Russian)

[22] Isaev, G. B., and Imanova, N. D. 2002. “A New Method for Immunomodulation in Patients with Peritonitis.” Saglamlyg 8: 10-3. (in Russian)

[23] Imanova, N. D. 2007. Correction Immunity with Saffron in Patients with Purulent-Septic Diseases. Dis. Baku. (in Russian)