

USE OF MEDICAL PRODUCTS WITH HYALURONIC ACID IN CHRONIC CYSTITIS TREATMENT

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Cystitis is one of the most frequent nosology forms of infectious and inflammatory diseases of the urinary tract, the main morphological substrate of which is an inflammatory process in the epithelium and stroma of the bladder wall, which is often associated with inflammation of the mucous membrane of the urethra (urethritis). Mainly urinary tract infections (UTI) such as cystitis are the most frequent option among women due to their anatomical features.

Approximately 50% of all women suffer at least one episode of UTI during life, and almost a third of all women have at least one episode of UTI till they are 24 [1].

But even taking into account the statistical data, it is worth remembering that cystitis is not only “women’s issue”.

Cystitis can occur in men of any age [2], in particular compromised by the presence of diabetes mellitus or immunodeficiency [3].

Classification of cystitis:

- – Primary;
- – Secondary;
- – Infectious;
- – Non-infectious;
- – Acute;
- – Chronic.

The last option, regardless of the etiology, occupies a special place in urological practice in connection with a particular approach to its diagnostics and treatment.

Chronic, or complications, cystitis occurs in the case, if there are more than three episodes in a year or two episodes in six months.

The causes of chronic cystitis may be abnormalities of the urinary tract, the presence of the increments concentrations of urinary tract, disorders of urine passage, the presence of a permanent source of bacteriuria.

The unifying element for all variants of chronic cystitis is permanent or transient damage of the mucous membranes, which can lead to an increase in the frequency of episodes, as well as to hyperplastic and occasionally dysplastic processes, such as polyps and keratinizing squamous metaplasia of urothelium (leukoplakia).

Atrophic and dystrophic changes in the bladder mucosa create favorable environment for the development and progression of epithelial damage, increase and change in the components balance of inflammatory cell infiltration in the stroma.

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Major diagnostic criteria are typical for cystitis clinical manifestation, the presence of bacteria, the frequency of the latest appearance and cystoscopy data.



In the case of chronic cystitis diagnosis the most attention is paid to determining the source of bacteria, microbiological research and assessment of mucosa state of the bladder.

Treatment of chronic cystitis mainly consists of causal antimicrobial therapy and prevention of further damage of the mucosa.

Current antimicrobial therapy is presented in details in the manual of the European Association of Urology (EAU, 2015). However, antimicrobial therapy does not eliminate all the issues in the problem of recurrence of cystitis, its chronic course

and often creates conditions for the *interstitial process* in the wall of bladder. As a result there appear the social suffering of the patient and the formation of other form of nosology, which is interstitial cystitis (IC). In this article we would like to pay special attention to the issue, which remains dilemmas in the treatment of cystitis, this is restoration of the protective properties of the bladder mucosa.

There are many drugs used to prevent damage of the mucosa and / or its recovery after myocardial inflammation. The need of such treatment is due to the fact that chronic cystitis, regardless of etiology there occurs permanent damage of urothelium, submucosa and lamina propria of the base wall of the bladder that leads to disease progression and worsening of symptoms. These drugs are in taken by means of instillation, i.e. directly into the bladder through a urinary catheter.

Preparations for the instillation of the bladder are classified according to their effect on the anti-inflammatory, enveloping and cauterizing. A desirable property is the availability of the antimicrobial activity. In recent years, there appeared intensive studies of a new group of solutions for instillation, which can strengthen tissue framework of the bladder wall, thus they create conditions for self-recovery of physiological barrier properties of the urothelium. One of the most commonly used members of this class of medical products are hyaluronic acid.

Hyaluronic acid is a substance from the group of non-sulfated glycosaminoglycans, which are the basis of connective tissue, ensuring the integrity and the basic physical and chemical properties of its own mucosa plate and submucosal base. Hyaluronic acid is also included in the epithelial cells (in particular, in the cells of specific subtype of epithelial, i.e. urothelium), and nervous tissue. Moreover, hyaluronic acid plays a significant role in the proliferation of cells.

In this connection, the substance finds increasing use in the treatment of chronic cystitis, as well as is able to prevent damage and ensure recovery of all components of the mucosa. We offer a detailed highlight of some of the research on the use of hyaluronic acid medical products for chronic cystitis.

Chronic cystitis in its morphological basis is interstitial inflammation, the main pathogenetic link of which is breach in urinary tissue barrier between hyperosmolar urine and intercellular substance of the bladder wall, allowing toxic products contained in the urine to penetrate into the stroma and cause an inflammatory response [4, 5]. IC manifests as painful bladder syndrome (PBS), which includes such symptoms:

- — compelling urge to urinate;
- — increased frequency of urination;
- — chronic pelvic pain.

Below is one of the research, which involved 121 women, aged from 17 to 83 with a diagnosis of IC / PBS, with an average duration of symptoms for 6.1 years. Participants carried out medical therapy by means of instillation

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of hyaluronic acid on a weekly basis until complete disappearance of PBS symptoms or their significant improvement. To avoid the risk of UTI associated with bladder catheterization, all patients had an appointment of 50 mg nitrofurantoin daily instillations. The results of the studies were based on patients' estimation of intensity of all symptoms manifestations in the context of PSB on the scale from 0 to 10 before and after the study.

The results showed an improvement in 85% of patients, reducing symptoms manifestations for 2 or more points on the above scale. Nineteen patients noted complete resolution of symptoms (0 on a scale) [6].

In another study in which 20 patients, aged 34-80, took part, the effectiveness of instillation of medical products with hyaluronic acid in reducing the intensity and the elimination of PSB symptoms was also evaluated [7].

The authors of the study concluded that the hyaluronic acid products within the long-term therapy are well-tolerated and effective in reducing the manifestations of IC / PSB.

The exceptional efficiency of hyaluronic acid in the treatment of Interstitial cystitis (IC) / Painful bladder syndrome (PBS) was demonstrated in a study of Aram Kim et al. [8], which included treatment of 33 women with symptoms of IC/PBS, who showed little or no response to local treatment of early instillation and antimicrobial therapy. All participants took 40 mg of hyaluronic acid by instillations on a weekly basis during 4 weeks. The study also reported the influence of preceding therapy features and the presence of ulcère de Fenwick-Hunner (as a characteristic manifestation of IC) on the effectiveness of therapy.

The study showed significant improvements that were observed among 61% of patients. The adverse effects of treatment were not noted, as well as the influence of the previous therapies and the presence of ulcère de Fenwick-Hunner – on the effectiveness of hyaluronic acid application.

Medical products on the basis of hyaluronic acid were widely used in many fields of medicine empirically, even before the mechanism of its action was studied in more detail. The latter is necessary for the recognition of the effectiveness of medical product for evidence-based medicine.

In light of this, laboratory tests that define protective and anti-inflammatory action of hyaluronic acid, carried out in vitro, deserve special attention.

A recent study carried out P. Rooney et al., the results of which were published in June 2015, studied in detail the mechanisms of effective beneficial effects of hyaluronic acid in cases of in vitro model of IC in combination of urothelial cells usage [9].

The study showed that hyaluronic acid is able to reduce the induced cytokine production significantly (in 4-5 times), reduce the intensity of or prevent altogether the development of the inflammatory process. The formation of sulfated glycosaminoglycans increase (in 2 times) was also noted, as well as and reduction of trans-epithelial permeability without damaging the natural barriers.

The findings, according to the authors, turn the use of hyaluronic acid medical products into the major clinical therapy vector in the therapy of IC.

In another, slightly earlier work, the purpose of which was to analyze the 13 laboratory researches, devoted to the mechanisms of hyaluronic acid action in case of the IC, the following data was represented.

Instillation of medical products on the basis of hyaluronic acid leads to:

- – a significant inhibition of the inflammatory process in the bladder wall;
- – reduction in the frequency and amplitude of bladder reductions;
- – the decrease in damage to the epithelium;
- – reduction of bacterial growth (in urine and tissue samples) [10].

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In general, in most countries around the world hyaluronic acid therapy is recognized as one of the essential and specific in cases of IC/PBS. For example, its application is included in the recommendations of the American Association of Urologists.

It is also interesting to analyze another study conducted in Austria, the purpose of which was to determine the costs of long-term treatment of IC/PBS by means of pathogenetic therapy, in particular with the use of hyaluronic acid medical products, in comparison with non-specific drug therapy. As a result, it was concluded that the use of specific drugs, such as hyaluronic acid had much lower cost in the framework of long time IC / PBS therapy [11].

In urological practice the derivative variant of the IC is reported in the context of other, exclusively male problem – radiation-induced IC, caused due to radiotherapy of malignant tumors in the prostate gland. In light of this problem, there are also many studies of effective application of hyaluronic acid medical product.

In one of them 20 patients of average age of 66 took part, they were diagnosed as suffering from prostate carcinoma after radiotherapy (total dose of 72-74 Gr) with symptoms of radiation-induced IC / PSB. This group was treated with the help of four weekly and two monthly instillations of hyaluronic acid medical products.

As a result, a significant improvement concerning symptoms was observed, in particular hematuria, pain, reduction in the frequency of urination. The total score in the evaluation of the severity of symptoms before and after application of hyaluronic acid was $2,70 \pm 0,47$ and $1,45 \pm 0,51$ respectively ($p < 0,01$ according to Wilcoxon test). Adverse effects were not observed in any of the patient.

Based on the results, the authors made the conclusion that the application of hyaluronic acid medical products is a safe and effective therapy for patients suffering from radiation-induced IC / PSB [12].

In conclusion, we can say that such a pathological condition as a chronic cystitis (IC / PBS) is common in urological practice and urgent medical problem, and the use of therapy by means of hyaluronic acid medical products instillation is effective and safe as well as low-cost solution in the long perspective.

On the Ukrainian market there was not adequate certified medical product for instillations based on hyaluronic acid for a long time, which made it impossible for local urologists to conduct an adequate and effective treatment of Interstitial cystitis / Painful bladder syndrome.

Today, the necessary medical product is available in Ukraine. On Ukrainian market medical product for intravesical intake "Instylan" by "Yuria Farm" company is introduced. It contains 80 mg of sodium hyaluronate (0.16%) in 50 ml of phosphate buffer, that shows high efficiency in clinical researches and has already been successfully applied by local specialists. Instylan is colorless, transparent, viscous gel of hyaluronic acid of non-animal origin; it is sterile, pyrogen-free, with a physiological pH of 7.3 for intravesical intake, having the storage period of 2 years. Its double pack is designed for use in a sterile environment; the package is equipped with a special attachment for the urethral catheter. Instylan aims at making a prosthetic appliance for deficient layer of the urinary bladder walls; it helps to relieve pain during urination, prevent imperative urgent urination, as well as frequent urination. The larger size of the Instylan molecules provides high barrier efficiency function between the urine and tissue. Unlike surface glycosaminoglycans, which are washed out with urine, Instylan creates stable impermeable barrier in the urothelial cells layer. Thus the effect of the painful symptoms reduction is achieved, whereas other treatments have failed in this case.

MAJOR CLINICAL EFFECTS OF THIS MEDICAL PRODUCT ARE CAUSED BY THE FOLLOWING FACTORS:

- – mechanical action: a barrier / lubrication;- moisturizing properties: high water binding;
- – moisturizing properties: high water binding;
- – healing properties: normalization of cell migration and proliferation;
- – filling defects of the bladder space;

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- – auxiliary function: interruption of the inflammatory cascade.



INDICATIONS FOR INSTYLAN PRESCRIPTION ARE:

- – chronic / recurrent cystitis;
- – interstitial cystitis;
- – overactive bladder;
- – temporary protection and restoration of the bladder mucosa during various manipulations (urethrocystoscopy, radiotherapy, and others);
- – irradiation cystitis;
- – urinary retention, or tumors formation caused by cystitis.

Instylan is intaken intravesically 1 time a week. Treatment includes from 4 to 12 instillations repeated once a quarter if necessary. Before using the product temperature should be at least 20°C, the bladder should also be empty. It is recommended to refrain from urinating at least 30 minutes after intake.

There are also many formulations based on the medical product. Here are three most commonly used of them in practice (International Painful Bladder Foundation):

1. The anesthetic mixture (created by Robert Moldwin): 0,5% bupivacaine and 2% lidocaine in a ratio of 1: 1 – with the total volume of 40 ml. 50 ml of sodium hyaluronate, 40 mg of triamcinolone and 80 mg of gentamicin or 1000 mg of ciprofloxacin were added to this solution. Application: the patient should refrain from urinating for 30 minutes. This mixture is used 1 time per week for 8 – 12 weeks.

2. Bupivacaine-steroid mixture (created by Nagendra Mishra): 0.5% 40 ml of bupivacaine, 50 mL of sodium hyaluronate, 2ml of dexamethasone. Application: the mixture should remain in the bladder for at least 20 minutes. It is used every 15 days, a total of 6 instillations. Further it is applied if necessary.

3. Mixture of Dimexidum (created by Philip Hanno): 5 ml of dimexide, 10 mg of kenalog, 50 ml of sodium hyaluronate. Application: 1 time per week for 6 weeks. Further – 1 time per month (if necessary).

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THUS, THE ADDITION OF ANTIMICROBIAL THERAPY FOR CHRONIC (INTERSTITIAL) CYSTITIS WITH THE HELP OF HYALURONIC ACID INSTILLATION IN BLADDER (INSTYLAN) IS AN IMPORTANT COMPONENT OF MODERN UTI TREATMENT, ENSURING:

- – the natural restoration of the barrier function of the bladder;
- – improving the efficiency of complex therapy for urinary tract infections;
- – the treatment of patients from the painful symptoms, and psychological dependence.

REFERENCES

1. Foxman B. *Epidemiology of urinary tract infections: incidence, morbidity, and economic costs // Dis. Mon.* — 2003. — 49(2). — P. 53-70.
2. Stamm W.E. *Urinary tract infections in young men // Urinary tract infections / Ed. by T. Bergan.* — Basel, Switzerland: Karger, 1997. — P. 46-7.
3. Funfstuck R. et al. *Urinary tract infection in patients with diabetes mellitus // Clin. Nephrol.* — 2012. — 77(1). — P. 40-8.
4. Parsons C.L., Lilly J.D., Stein P. *Epithelial dysfunction in nonbacterial cystitis (interstitial cystitis) // J. Urol.* — 1991. — 145. — 732-735.
5. Hohlbrugger G. *Leaky urothelium and/or vesical ischemia enable urinary potassium to cause idiopathic urgency/frequency syndrome and urge incontinence // Int. Urogynecol. J. Pelvic Floor Dysfunction.* — 1996. — 7. — 242-255.
6. Riedl C.R., Engelhardt P.F., Daha K.L., Morakis N., Pflüger H. *Hyaluronan treatment of interstitial cystitis/painful bladder syndrome // International Urogynecology Journal.* — 2007.
7. Kallestrup E.B., Jorgensen S.S., Nordling J., Hald T. *Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product // Scand. J. Urol. Nephrol.* — 2005. — 39(2). — 143-7.
8. Kim A., Lim B., Song M., Choo M.-S. *Pretreatment Features to Influence Effectiveness of Intravesical Hyaluronic Acid Instillation in Refractory Interstitial Cystitis/Painful Bladder Syndrome // Int. Neurourol. J.* — 2014. — 18. — 163-167.
9. Rooney P., Srivastava A., Watson L., Quinlan L.R., Pandit A. *Hyaluronic acid decreases IL-6 and IL-8 secretion and permeability in an inflammatory model of interstitial cystitis // Acta Biomater.* — 2015 Jun. — 19. — 66-75.
10. Cicione A., Cantiello F., Ucciero G., Salonia A., Madeo I., Bava I., Aliberti A., Damiano R. *Restoring the glycosaminoglycans layer in recurrent cystitis: experimental and clinical foundations // Int. J. Urol.* — 2014 Aug. — 21(8). — 763-8.
11. Riedl C., Engelhardt P., Schwarz B. *Treatment costs of bladder pain syndrome/interstitial cystitis in Austria: a pharmaco-economic approach following current guidelines // Clin. Drug Investig.* — 2013 Oct. — 33(10). — 737-42.
12. Kouloulias V., Mosa E., Fotineas A., Beli I., Asimakopoulos C., Chaldeopoulos D., Chrysofos M., Siatelis A.,

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hyaluronic acid-based sterile solution for intravesical application

- Kelekis N. Use of Hyaluronic Acid (Cystistat) for the Treatment of Late Radiation Induced Cystitis in Patients after Prostate Irradiation // *J. Bioequiv. Availab.* — 2014. — 6. — 018-022.
13. Altarac S., Papes D. The treatment of chronic cystitis by hyaluronic acid and chondroitin sulphate // *Lijec. Vjesn.* — 2011 Sep-Oct. — 133 (9–10). — 354-5.
14. Damiano R., Cicione A. The role of sodium hyaluronate and sodium chondroitin sulphate in the management of bladder disease // *Ther. Adv. Urol.* — 2011 Oct. — 3(5). — 223-32.
15. Schulz A., Vestweber A.M., Dressler D. Anti-inflammatory action of a hyaluronic acid-chondroitin sulfate preparation in an in vitro bladder model // *Aktuelle Urol.* — 2009 Mar. — 40(2). — 109-12.
16. Parsons M., Tooze-Hobson P. The investigation and management of interstitial cystitis // *J. Br. Menopause Soc.* — 2005 Dec. — 11(4). — 132-9.
17. Lv Y.S., Yao Y.S., Rong L., Lin M.E., Deng B.H., Xie Y., Huang H., Lin T.X., Xu K.W., Huang J. Intravesical hyaluronidase causes chronic cystitis in a rat model: a potential model of bladder pain syndrome/interstitial cystitis // *Int. J. Urol.* — 2014 Jun. — 21(6). — 601-7.
18. Porru D., Campus G., Tudino D., Valdes E., Vespa A., Scarpa R.M., Usai E. Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid // *Urol. Int.* — 1997. — 59. — 26-29.
19. Van de Merwe J.P., Nordling J. Interstitial cystitis: definitions and confusable diseases. ESSIC meeting 2005, Baden // *Eur. Urol. Today.* — 2006. — 18. — 6, 7, 16, 17.
20. Karsenty G., AlTaweel W., Hajebrahimi S., Corcos J. Efficacy of interstitial cystitis treatments: a review // *EAU-EBU Update Series.* — 2006. — 4. — 47-61.