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## USE OF MEDICAL PRODUCTS WITH HYALURONIC ACID IN CHRONIC CYSTITIS TREATMENT

*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.

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, micro-

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biological 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 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].

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).

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., Ma-deo 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 pharmacoeconomic approach following current guidelines* // *Clin. Drug Investig.* — 2013 Oct. — 33(10). — 737-42.
12. Kouloulis V., Mosa E., Fotineas A., Beli I., Asimakopoulos C., Chaldepoulos D., Chrysofos M., Siatelis A., 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.

15. 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.
16. 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.
17. Parsons M., Toozs-Hobson P. *The investigation and management of interstitial cystitis* // *J. Br. Menopause Soc.* — 2005 Dec. — 11(4). — 132-9.
18. 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.
19. 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.
20. 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.
21. Karsenty G., AlTaweel W., Hajebrahimi S., Corcos J. *Efficacy of interstitial cystitis treatments: a review* // *EAU-EBU Update Series.* — 2006. — 4. — 47-61.