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The modern approach to intravesical therapy of chronic cystitis

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The difficulty of treating patients with chronic recurrent cystitis is caused by various factors like the virulence of uropathogenic Escherichia coli as well as the state of the local resistance of the bladder's mucosa and their interaction. Hyaluronic acid instillations used in the treatment of patients with chronic cystitis led to pronounced positive clinical dynamics in 95% of patients, as well as to more than a 2 fold reduction in the number of recurrences of cystitis, which greatly improved the quality of life of patients. The results allow us to recommend the use of intravesical sodium hyaluronate for the treatment of various forms of chronic cystitis.

Key words: *chronic cystitis, intravesical therapy, sodium hyaluronate.*

Cystitis is one of the most common urological diseases. Annually, about 3 million patient visits to doctors in the USA alone are associated with various forms of cystitis.

Bacterial infection is the most common cause of chronic cystitis. About 40-50% of women have experienced acute cystitis once in their lifetime, 20-30% of women experience a recurrence within 3-4 months after the first episode of a urinary tract infection. About 10-20% of them suffer from recurrent cystitis throughout their life. The diagnosis of recurrent cystitis involves 2 exacerbations within 6 months or 3 exacerbations during the year, which significantly affects not only the quality of life of patients, but has a large social and economic impact on society as a whole [1].

Recently, there exist experiments confirming the formation of intracellular bacterial communities in urothelium cells, which ensures the persistence of Escherichia coli in the urinary tract [15]. Difficulties in treating patients with chronic recurrent cystitis are caused by various factors like the virulence of uropathogenic Escherichia coli as well as the state of the local resistance of the bladder's mucosa and their interaction. A uropathogenic Escherichia coli is able to simulate the immune response of macroorganisms. There are well-known immunomodulatory roles of sexually-transmitted intracellular pathogens, which create prerequisites for the development of bacterial cystitis in women [2].

Atrophic processes are of great importance in the development and support of chronic cystitis in women during the postmenopause period. The most severe conditions which are also manifestations of chronic cystitis include cystalgia and interstitial cystitis, which are resistant to standard conservative therapy [8].

In case of interstitial cystitis, changes of phases of the course of inflammatory processes occur, thus leading to a severe pain syndrome and a decrease in bladder capacity with increasing dysuria. This clinical picture and accompanying morphological manifestations indicate the cyclical nature of the disease with frequent changes in episodes of remissions and exacerbations [9].

Chronic cystitis is a disease characterized by a long-standing inflammatory reaction in the bladder tissue. The reason for inflammatory infiltration in the mucosa and submucosal layers of the bladder wall is due to the damage of the intermediary substance of the connective tissue due to various causes - both of congenital and acquired character. Regardless of these reasons, the result is a violation of the physiological regeneration process of the bladder's epithelium and barrier function of the transitional epithelium [12]. These changes lead to dysregeneratory processes in the urothelium, followed by a change in the physiologically-based distribution of the subpopulations of mononuclear cells. The above changes can be interpreted as the interstitial inflammation with manifestation of glycosaminoglycan deficiency [3].

Glycosaminoglycans and in particular zinc hyaluronate as the biopolymers of the mucopolysaccharide type, are the most important components of connective tissues, skin and mucous membranes. Due to its high hydrophilicity, it readily forms a dispersion matrix with water molecules, which is important in maintaining protective mechanisms as well as the elasticity of the skin and mucous membranes [4, 10]. The most important fact is that hyaluronic acid enhances the migration of fibroblasts. The local concentration of hyaluronic acid increases in the process of tissue regeneration: this creates optimal conditions for the activation of the migration and proliferation of cells involved in tissue regeneration. The local microcirculation improves as a result of such angiogenic properties. In cases of pathological processes, the concentration of hyaluronic acid in tissues decreases due to such imbalance and the recovery process slows down. In case of interstitial cystitis, the concentration of hyaluronic acid in the bladder's mucous membrane decreases, thus leading to a decrease in the proliferation and regeneration of epithelium, which can be influenced by the local application of hyaluronic acid. Naturally, hyaluronic acid occurs in the form of sodium salts; it is a homopolymer of M-acetyl-O-glucosamine and D-glucuronic acid, 1-3-beta-linked. The molecular mass ranges from 1000 to several million Daltons [13].

Studies conducted in recent years have found that hyaluronic acid binds to a large number of molecules in aqueous solutions with the formation of a dense molecular “sieve”. The dispersion matrix forms canaliculi for selective diffusion of water-soluble molecules. Hydrophobic areas regularly repeat on the molecule, that facilitates the interaction between cellular membranes and hydrophobic type proteins [11]. It should be noted that hyaluronic acid controls the water content in the extracellular fluid, counteracting bacterial penetration. In addition, it binds to cations and significantly affects cell mobility and tissue regeneration [4].

Treating recurrent infections of the lower urinary tract is a great challenge. Prolonged courses of antimicrobial therapy with oral doses give a positive effect only during the treatment, while frequent recurrences of infection are observed again after discontinuation of therapy [5].

Moreover, such tactics lead to the development of microorganisms which are resistant to antimicrobial drugs [6, 14].

Vaccination therapy has so far failed to fulfil expectations. Recurrent cystitis is difficult to treat conservatively, thus driving numerous researchers to look for new therapies.

Intravesical usage of hyaluronic acid is a promising method, but it requires the carrying out of several randomized trials.

All of the above determine the relevance of this topic.

MATERIALS AND METHODS

A total of 95 women were examined with a preliminary diagnosis of chronic cystitis, cystalgia, interstitial cystitis. Generally, patients reported the same complaints of constant or periodic dysuria, pollakiuria, urethralgia, lower abdominal pain, heavy weight above the pubis, increasing with the bladder filling and reaching the greatest intensity at the end of urination, a feeling of incomplete urinary bladder emptying, urgency, sometimes, a hyperactive bladder. Based on a complete physical examination, 30 women were selected from the 95 patients, among which 3 groups were distinguished according to the developed examination card (the presence or absence of signs of urinary tract infection, including sexually transmitted infections were taken into account except for complaints, anamnesis, physical examination, laboratory data) as follows:

I. Patients with a urinary tract infection, i.e. with recurrent bacterial cystitis and, in particular, with sexually transmitted infections, - 10 (33.3%) patients.

II. Patients with dysuria in post-menopause, without laboratory confirmation of a urinary tract infection - 11 (36.7%) patients.

III. Patients with interstitial cystitis - 9 (30%) patients.

For the examination of patients, an individual registration card was developed, which included the following: age, sex, nosological entity of the disease, severity of the course of the disease, anamnestic data, complete blood count and urine analysis, bacterial urinalysis on the flora and susceptibility to antimicrobial drugs, microscopy of smears from the urethra, vagina and cervix, PCR-based diagnostics for sexually transmitted infections. Examinations were performed on a gynecological examination chair (according to indications – consulted by a gynecologist), ultrasonography of the kidneys and bladder, urodynamic examination and excretory urography (according to indications). Urination diaries and pain visual analogue scale (VAS) were used to assess the severity of dysuria and pain syndrome.

Comparative analyses of the quantitative changes which characterize the clinical and laboratory as well as functional states of the urinary system were performed through descriptive statistics using the nonparametric Wilcoxon test. The statistical method of the chi-squared (x^2) criterion was used in the analysis of qualitative characteristics. In describing the qualitative characters of the data distribution, the standard error of the proportion (m) was used in the calculations as well as the standard deviation (o) was used to assess the quantitative characteristics. Processing and graphical representation of data were carried out using "Statistica 6.0" and "Excel 2003" as statistical computer programs.

STUDY RESULTS AND DISCUSSION

Various states were identified during the complete physical examination of 30 patients with chronic recurrent cystitis. Patients are divided into three nosological groups:

- Group I - patients with chronic recurrent bacterial cystitis.
- Group II - patients with post-menopausal chronic cystitis.
- Group III - patients with nonbacterial forms of chronic cystitis.

Despite the different ages of patients in the 3 study groups coupled with the presence or absence of bacterial infection of the urinary tract and sexually transmitted intracellular pathogens, all patients had a fairly similar pronounced clinical symptomatology with frequent recurrences of the disease and a low quality of life. All patients had a fairly long experience of treatment concerning their disease without a satisfactory effect. The treatment consisted in the administration of antimicrobial, non-steroidal anti-inflammatory, sedative drugs, antidepressants, antihistamines, etc. In addition to systemic pharmacotherapy, they were given intravesical instillations of various substances, such as collargol, protargol, sea buckthorn oil, antibiotics and local anesthetics. In addition, various physiotherapeutic methods were used in the treatment of our patients. All these surely decreased recurrences of the disease for a certain time, reduced the severity of clinical symptoms and somehow improve the quality of life of patients.

While analyzing the possible mechanisms of the etiology and pathogenesis of the disease in the three nosological groups after a thorough study of clinical, cystoscopic and morphological characteristics, we found a number of features of the state of bladder wall and its epithelium. Patients of all groups had cystoscopic signs of urothelium lesion.

As a result of the endoscopic examination of the 30 patients, hyperemia of the mucous membrane of various degrees in the area of the vesical triangle, neck of the urinary bladder and internal urethral opening were detected in 14 (46.7%) of them. In these cases, this symptom was expressed to a greater extent in the groups I and III. Glomeruli were detected during cystoscopy in 8 patients, which accounted for 26.7% of all patients. When analyzing this criterion, depending on the nosological group, it was found that this symptom was significantly more frequent in Group III than in patients from other groups. We detected Hunner's ulcer only in two patients (6.7%), who all belonged to the third nosological group. Urinary bladder's mucous membrane vascular injection took place in 10 patients, which amounted to 33.3% of patients of all groups. To a lesser extent, this symptom was expressed in the second group of patients. In a small percentage of cases (6.7%), we found a pseudopolyposis in the neck of the bladder. This symptom was distributed almost evenly between patients of all groups. It was not possible to detect statistically significant differences. We found signs of atrophy of the urinary bladder's mucous membrane in 6 (20%) patients. This symptom prevailed in patients of the second nosological group, i.e. in patients of postmenopausal age; it reached 87% in this group while in the other groups this indicator did not exceed 7.3%. The differences observed with this criterion were statistically significant ($p < 0.05$). Also, atony of the bladder internal sphincter was reported in the second nosological group with a high statistical significance ($p < 0.05$).

In the course of the study, we investigated the efficacy, safety and tolerability of the intravesical istillations of sodium hyaluronate (Instylan 80 mg/50 ml, Yuria-Pharm, Ukraine) in the treatment of patients with chronic recurrent bacterial cystitis, chronic postmenopausal cystitis and in patients with nonbacterial forms of chronic cystitis, i.e. in patients with confirmed deficiency of the glucosaminoglycan layer of the bladder.

The inclusion criteria for the study group, in addition to the results of the morphological study, also include the requirement of non-participation in other studies, and non-receipt of treatment by intravesical instillations for 6 months before inclusion in to the study group.

All 30 patients were prescribed a course of 10 intravesical instillations of 50 ml (80 mg) of sodium hyaluronate solution once a week. After individual urinary bladder emptying and external genitalia preparation with 0.2% chlorhexidine bi-gluconate solution, bladder catheterization was carried out with a sterile urethral catheter. After the administration of Instylan, patients were advised not to empty the bladder for one or more hours to increase exposure.

Within a year after the end of treatment, the indicator of the number of cystitis recurrences decreased significantly by more than 2 folds for all groups of patients, which improved the quality of life of our patients.

The number of exacerbations decreased by 6.4 times in all three groups: in Group I - by 5.8; in Group II - by 4.5 and in Group III - by 6.4 exacerbations per year (Table 1).

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Table 1

Cystitis recurrence rate before and after the treatment (p <0.01)

Results (M±a)	All patients, n=30	Group I, n=10	Group II, n=11	Group III, n=9
The average number of cystitic recurrences (per year) before the treatment, number of cases	10.96±7.3	11.1±6.5	9.3±4.7	12.5±5.9
After the treatment, number of cases	4.56±5.6*	5.3±4.1*	4.8±3.8*	6.1±4.6*

Note. * The difference is statistically significant before and after the treatment.

The analysis of the nature of complaints of patients in the nosological groups with regards to their dynamics, before and after the treatment, revealed the following: the frequency of pollakiuria in the study groups decreased by 3.8 times (by 63.7%); while in group I, the indicator decreased by 4 times, in group II - by 5 times, and in group III - by 3 times. The frequency of nocturnal pollakiuria decreased by 3.1 times (i.e. by 50%): in group I - by 4 times, in group II - by 6 times, and in group III, the frequency of night pollakiuria decreased by 2.7 times. The frequency of urgency to urinate decreased by 5 times (by 53.4%) in the three groups after treatment. This indicator decreased by 7 times for Group I, by 8 times - for Group II and by 2.5 times - for the nosological Group III patients. All patients from the three nosological groups complained of pain above the pubis before the initiation of treatment. This indicator decreased by 3.1 times (by 63.3%) after treatment. Pain episodes above the pubis decreased by 3.3 times in Group I, by 5 times in Group II and by 2.5 times in Group III.

Before the start of treatment, pain during bladder filing affected 22 (73.3%) patients while at the end of treatment, this indicator decreased by 2.7 times (by 46.6%). This indicator decreased by 3.3 times in Group I, by 3.5 times in Group II and by 2.5 times in Group III. The frequency of discomfort and burning with urination decreased by 3.5 times (by 50%) in the three groups after the initiation treatment. This indicator decreased by 6 times in Group I, by 2.7 times in Group II and by 3.5 times in Group III. The frequency of dyspareunia after treatment decreased in all three groups and by 2.7 times (by 40%) for groups I and II, the frequency of pain during sexual intercourse decreased by 3 times, and by 2.3 times in Group III. The duration and intensity of the above complaints caused emotional distress of patients with chronic cystitis in 60% of cases. Most often, they did not believe in the success of the proposed treatment at the beginning, having had an unfavorable long-term experience of previous therapy. Emotional distress was clearly pronounced in all three groups though no statistically significant differences were found. However, the frequency of this indicator decreased by 2.7 times (by 40%) for all three groups after the initiation of treatment. This indicator decreased by 3 times in Group I, by 2.3 times in Group II and by 3 times in Group III (Table 2).

Table 2

Cystitis recurrence rate before and after the treatment (p <0.01)

Complaints of patients before and after treatment	All groups, n=30		Group I, n=10	Group II, n=10	Group III, n=10
	Absolute number	%	Absolute number	Absolute number	Absolute number
Pollakiuria					
Before treatment	27	90	8	10	9
After treatment	7*	23,3	2*	2*	3*
Nocturnal pollakiuria					
Before treatment	22	73,3	8	6	8
After treatment	6*	20	2*	1*	3*
Urgency					
Before treatment	20	66,7	7	8	5
After treatment	4*	13,3	1*	1*	2*

Note. * The difference is statistically significant before and after the treatment.

Cystitis recurrence rate before and after the treatment (p <0.01)

Table 2

Complaints of patients before and after treatment	All groups, n=30		Group I, n=10	Group II, n=10	Group III, n=10
	Absolute number	%	Absolute number	Absolute number	Absolute number
Pain above the pubis					
Before treatment	28	93,3	9	10	9
After treatment	9*	30	3*	2*	4*
Pain during bladder filling					
Before treatment	22	73,3	6	7	9
After treatment	8*	26,7	2*	2*	4*
Discomfort and burning sensation with urination					
Before treatment	21	70	6	8	7
After treatment	6*	20	1*	3*	2*
Dyspareuria					
Before treatment	19	63,3	6	6	7
After treatment	7*	23,3	2*	2*	3*
Emotional distress					
Before treatment	19	63,3	6	7	6
After treatment	7*	23,3	2*	3*	2*

Note. * The difference is statistically significant before and after the treatment.

While analyzing the complaints that patients with chronic cystitis of all three nosological groups presented before and after the end of treatment, attention was drawn to the fact that the average volume of urination (in ml) increased by 45.4 ml in general; in Group I by 34.2 ml, in Group II by 60.3 ml, in Group III by 61.2ml.

The frequency of urination per day decreased by 2.6 times in general: by 2.6 times in Group I, by 2.6 times in Group II and by 2.1 times in Group III.

The frequency of nocturnal urination decreased by 2.35 times in general; by 2.45 times in Group I, by 2.2 times in Group II and by 2.3 times in Group III (Table 3).

Table 3

Dynamics of urination diary data in patients before and after treatment (p <0.05)

Index	Output data (M ± a)			
	All groups, n=30	Group I, n=10	Group II, n=11	Group III, n=9
The average volume of urination, ml				
Before treatment	137.3±39.6	154.9±73.1	138±51.4	108.3±54.3
After treatment	182.7±71.2*	189.1±86.7*	198.3±64.1*	169.5±48.2*
The frequency of urination per day				
Before treatment	15.1±2.1	14.0±3.9	13.5 + 4.0	18.9±9.3
After treatment	5.8±2.0*	5.3±1.9*	5.2±2.0*	8.9±3.1*
The number of nocturnal urination	4.7±0.8	5.4±2.9	3.3±1.5	6.4±1.9
After treatment	2.0±0.3*	2.2±0.6*	1.5±0.4*	2.8±1.1*

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During bladder filling, the pain visual analogue scale (VAS) and analyzing the data obtained, it was found that pain disturbed more or less patients from all three nosological groups. There was a pronounced positive dynamic after the treatment: in some patients the pain completely disappeared, while a significant reduction in pain syndrome was noted in other patients (Table 4).

Table 4

Severity of pain syndrome in nosological groups before and after treatment, scores (p <0.05)

Severity of pain	Group I, n=10		Group II, n=11		Group III, n=9	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Insignificant	10	60*	30	70*	20	80*
Average	30	20*	40	20*	40	10*
Intense	30	10*	20	0*	30	10*
Severe	30	10*	10	0*	10	0*

*Note.** - The difference is statistically significant.

In the post-treatment examination phase, attention was drawn to the reduction in the number of samples with treatment-relevant bacilluria, i.e. by 4 times (by 20%) based on all three nosological groups. Leukocyturia decreased by 3.5 times (by 33.4%) in all three groups. The most significant changes were in the parameters of patients of nosological Group I. In the first group of patients with bacterial cystitis, the most common pathogen was Escherichia coli (88.5%) while Enterobacter spp., Enterococcus spp., K. Pneumoniae, P. aeruginosa were detected in a small percentage of cases (1.9%). Patients of this group underwent antimicrobial therapy according to the sensitivity data of pathogens.

25 (83.33%) patients noted a significant improvement in their state of health, reduction in complaints; a decrease in the frequency of urgency as well as increase in the intervals between cystitis exacerbations. 5 patients (16.97%) had no improvement in their clinical status.

The drug showed good safety and tolerability. Only one patient (3.33%) refused to administer the drug due to the burning. Side effects, allergic reactions during the study period have not been reported.

CONCLUSIONS

1. The use of Instylan instillations in the complex therapy of patients with chronic cystitis showed pronounced positive clinical dynamics in 95% of patients.

2. The use of Instylan showed decrease in the number of cystitis recurrences by more than 2 folds, which significantly improved the quality of life of patients.

3. The results obtained allows us to recommend the administration of intravesical sodium hyaluronate in the therapeutic plan for various forms of chronic cystitis accompanied by a deficiency of the glucosaminoglycan layer.

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