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Practical Application of Instylan – Modern Protector of Urinary Bladder Mucosa

The inner surface of the urinary bladder is covered by glycosaminoglycan layer (GAG-layer).

The main task of this layer is to bind water, forming a thin protective film between urine and the surface of the urinary bladder. This protective film prevents bacteria and other irritants, contained in the urine (e.g., potassium ions, calcium microcrystals, protease), from affecting the urinary bladder that can cause inflammation and pain [1].

It has been proved that the GAG-layer simultaneously performs several important functions: it protects the deeper layers of the urinary bladder walls from irritants' penetration from the urine; prevents giving rise and increase of inflammation, as well as reduces the degree of pain caused by inflammation [1, 21].

Urothelium defects are the cause of many chronic diseases of the urinary tract (interstitial cystitis, recurrent bacterial cystitis, radiation cystitis, overactive urinary bladder, etc.), accompanied by the appearance of such symptoms as urgent and frequent urination, urinary incontinence, pain during urination, syndrome of urinary bladder chronic pain. Such patients are largely limited in their daily activities and suffer from reduced quality of their life [2, 3].

The mechanism of pain in the bladder:

1. Damage of GAG-layer.
2. The destruction of the epithelial layer by aggressive structures.
3. Inflammation in sub-epithelial structures.
4. Activation of C-fibres and release of Neuropeptides.

5. Neurogenic inflammation.

6. Progression of fibrosis, scarring, shrinkage of the urinary bladder.

Chronic inflammation of the urinary bladder can lead to the replacement of its muscular wall by fibrous tissue, as well as sclerosis and ultimately to the development of microcysts [21]. To solve this problem, the therapy designed to restore the protective layer of urothelium is recommended.

Today in clinical practice different treatment strategies are used. They suggest prescription of antidepressants, antihistamines, cysteine, leukotrienes receptors antagonists, internal bladder instillation of dimethyl sulfoxide to patient, but when the pain syndrome is present, opioid analgesics are prescribed. In difficult cases surgery can be performed (augmentation of urinary bladder, cystectomy with application of urine derivation methods), which is the only method of solving this problem [13-15].

In recent years the application of therapy that helps to restore the GAG-layer is actively studied.

The most studied among glycosaminoglycans are hya-

luronic acid, chondroitin sulfates, dermatan sulfates, keratan sulfates and heparan sulfates that compose skin, tendons, cartilage, joints, providing mechanical strength and elasticity of inner organs, as well as elasticity of their joining [12].

In particular, hyaluronic acid is a glycosaminoglycan which, according to its chemical nature, is a branched chain of repeated disaccharide components (Fig. 1). At pH 7.0 level carboxyl groups of hyaluronic acid are fully ionized, bearing a negative charge and interacting with water molecules to form jelly-like matrix [12].

The name "Hyaluronic acid" was first suggested in 1934 by K. Meyer and J. W. Palmer, who identified this substance of the vitreous body of the eye. Its name comes from the Greek word hyalos - "glassy" and "uronic acid" [11].

It has been proved that glucosamine, chondroitin and hyaluronic acid have anti-inflammatory and analgesic effects, as well as water-containing biopolymer with silver ions has antibacterial effect, and the hyaluronic acid has derma-protective effect.

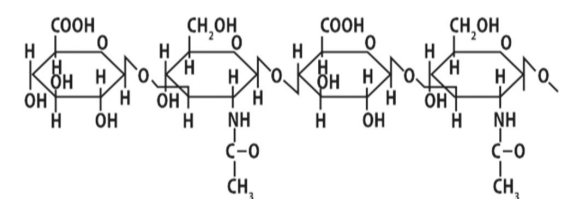


Fig. 1. Fragment of Hyaluronic acid structure

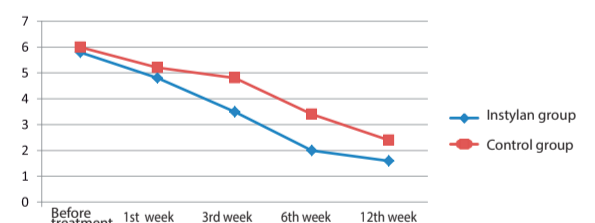


Fig. 2. The average frequency of nocturia in studied groups

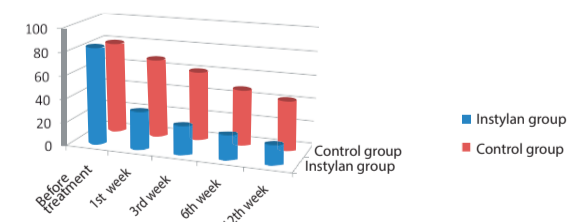


Fig. 3. Comparative assessment aimed at determination of residual urine

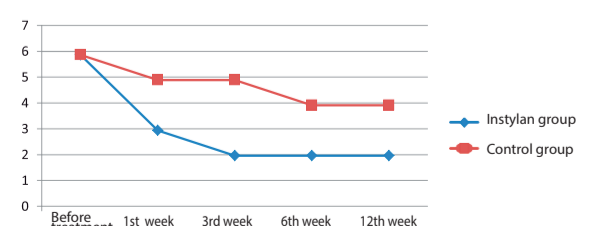


Fig. 4. The index of quality of life (L)

Table 1. Clinical Research of Hyaluronic Acid in Urology

Research	No of patients	Diagnosis	Prescription	Result
Miodosky et al. (2006) [8]	7	Hemorrhagic cystitis	4 weekly instillations + a monthly dose	Among 6 out of 7 patients – satisfactory result
Daha et al. (2005) [16]	48	Interstitial cystitis	10 weekly instillations	Improvement was observed in 41 case
Gupta et al. (2005) [17]	36	Interstitial cystitis	6 weekly instillations	20 patients had a positive response for treatment
Kallestrup et al. (2005) [18]	20	Interstitial cystitis	4 weekly instillations + 2 monthly doses	Among 40% of patients nocturia symptoms decreased, among 30% – pain intensity decreased. Thus, 13 patients showed positive result of this treatment
Constantinides et al. (2004) [19]	40	Recurrent inflammatory manifestations of the lower urinary tract	4 weekly instillations + 2 monthly doses	During 5 months – no relapses among 40 patients, during up to 2 months – among 28 patients
Leppilahti et al. (2002) [20]	11	Interstitial cystitis	4 weekly instillations	During 1 year 8 patients reported positive result
Morales et al. (1997) [8]	25	Interstitial cystitis	4 weekly instillations + a monthly dose during 1 year	71% patients showed positive response for treatment

Table 2. Structure of the disease among studied

Diagnosis	Number of cases, n (%)
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Radiation cystitis	16 (43%)
Bladder cancer	15 (32%)
Interstitial cystitis	6 (16%)

Table 3. Structure of the prescriptions in the control groups

Number of patients who received Instylan intravesically, n			Number of patients who received the basis therapy, n		
18			19		
Radiation cystitis	Interstitial cystitis	TUR of the bladder wall	Radiation cystitis	Interstitial cystitis	TUR of the bladder wall
6	3	9	8	4	7

Table 4. The frequency of urination

Control Period	Average number of urination per day, n		Average number of painful urination per day, n	
	Instylan group	Control group	Instylan group	Control group
Before treatment	12,4	12,8	8,8	9,1
1st week	9,0	12,0	6,2	8,8
3rd week	8,4	11,8	6,0	7,2
6th week	8,0	11,2	2,4	4,3
12th week	7,8	10,4	1,6	2,8

Table 5. Average values of uroflowmetry research data

Control Period	Instylan group			Control Period	Control group		
	Speed max, ml/min	Average speed, ml/min	Volume, ml		Speed max, ml/min	Average speed, ml/min	Volume, ml
Before treatment	10,2	8,2	128	Before treatment	11,0	8,8	116
1st week	12,4	10,6	188	1st week	12,2	10,4	142
3rd week	13,8	12,0	224	3rd week	14,0	12,2	158
6th week	15,0	13,4	248	6th week	15,0	13,0	182
12th week	18,2	14,6	266	12th week	17,8	14,2	204

The Use of Hyaluronic Acid in Medicine

Given that hyaluronic acid comprises many tissues (skin, cartilage, vitreous body of the eye), it is used for curing diseases connected with these tissues: in ophthalmology (cataract treatment) [5] orthopedics (osteoarthritis, osteochondrosis, spondylosis, periartthritis) [4], cosmetology and cosmetic surgery (as intradermal injection) [6] stomatology (treatment of gingivitis), pulmonology (asthma treatment) [7], urology (treatment of cystitis, uric ureter reflux) [8-10].

Clinical research of intracystic application of hyaluronic acid instillations [22] is presented in Table 1. In order to assess the effectiveness of 50 mg / 80 mg sodium hyaluronate (Instylan, "Yuria-Pharm") intracystic use in the treatment of inflammatory changes of the lower urinary tract, the authors of this article conducted the research, based on the Department of Plastic and Reconstructive Oncurology, SI "National Cancer Institute" from March to June 2015. The research involved 37 patients, 18 of whom were treated with the help of intracystic use of 80 mg sodium hyaluronate (Instylan). The control group consisted of 19 patients who underwent basic antibacterial and anti-inflammatory therapy. The duration of observation was 3 months. First medical examination of patients coincided with the day of the treatment start, and assessment of treatment efficiency was done during the following visits (2-8).

Intracystic administration of Instylan (50 mL of 0.16% sodium hyaluronate solution) was carried out according to the instructions once a week for 4 – 6 weeks with its further intake once a month. Instillation was performed with the help of urethral catheter in an ambulatory care clinic with observance of aseptic rules.

The study evaluated the dynamics of clinical symptoms, complaints about frequent, painful urination, urgent urination, urge incontinence, nocturia; uroflowmetry indices, residual urine volume, quality of life.

The study involved 20 (54%) men and 17 (46%) women, whose average age was 42.5 years. The research group consisted of the highest number of patients with radiation cystitis - 43% (Table. 2).

The division of patients was based on pathological conditions that were treated with the help of intracystic administration of Instylan. Concerning radiation cystitis, 6 patients were treated with 6 weekly intracystic instillations; 9 patients took only one Instylan instillation after removal of urethral catheter in case of the bladder wall transurethral resection (TUR); 3 patients had intracystic instillations every 4 weeks with regard of treating interstitial cystitis (Table. 3).

The average frequency of urge incontinence per day among patients who took Instylan decreased from 12.4 to 7.8 times comparing to the control group: from 12.8 to 10.4 times a day during 3 months of the study.

The most pronounced decrease of dysuric manifestations occurred within 1-6 weeks of treatment (Table. 4). In particular, 9 patients who took only one Instylan instillation after removal of urethral catheter, reported a significant reduction in the frequency of urge incontinence from 10.2 to 4.8 times compared to the control group: from 9.8 to 6.6 times during the first week after instillation.

By 12 weeks of the study the frequency of nocturia in patients who applied intracystic instillations of Instylan decreased by 72.4% (from 5.8 to 1.6 times) compared to the control group of patients - 60% (from 6 to 2.4) (Figure 2).

According to uroflowmetry indices, maximum and average speed of urination in both study groups did not differ significantly, but the average volume of urine in the control group of patients increased by 88 ml in the group of patients that took Instylan - 138 ml. Moreover, in the Instylan group the urination act volume increased sharply during the first 3 weeks of treatment (Table. 5).

Given the research data, in the period of up to 12 weeks of observation the average volume of residual urine decreased in both groups: 16 ml - in the study group of patients, to 42 ml - in control group. It is particularly worth noting that patients who took Instylan reported that after the first week of treatment average volume of residual urine reduced from 84 to 32 ml (more than 2.5 times) compared to the control group - from 80 to 68 ml (Fig. 3).

After 3 weeks of the study passed 16 (83%) patients, who were treated with the help of Instylan, rated satisfactory quality of life (quality of life index L = 2) compared to the control group (index of quality of life L = 4), which in its highest position did not achieve satisfactory level until the end of research (Fig. 4).

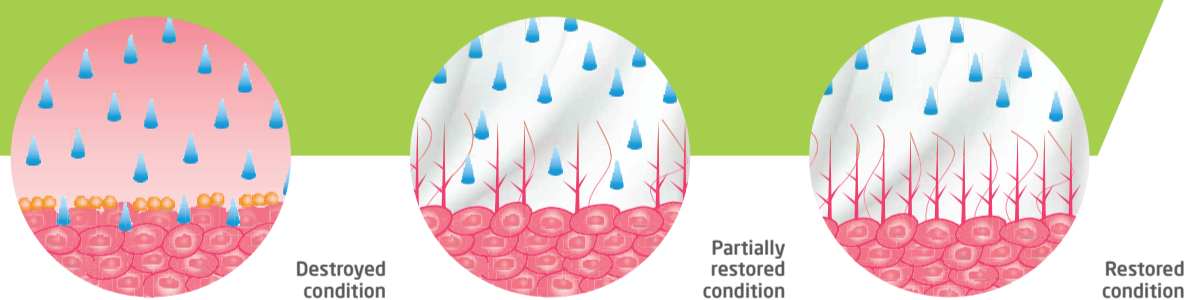
Thus, intracystic application of sodium hyaluronate (Instylan) is an effective treatment for various forms of chronic cystitis in the early postoperative period after transurethral resection of the bladder wall. Such result is achieved by reducing the effects of dysuria, nocturia frequency, residual urine volume, increased volume of urination that ultimately provides significant increase of patients' quality of life.

References can be found in editorial office

INSTYLAN

STERILE SOLUTION BASED ON HYALURONIC ACID
FOR INTRAVESICAL IRRIGATION

NATURAL protection of barrier function of urinary bladder in case of cystitis



- ▼ Hyaluronic acid-based sterile solution for intravesical application
- ▼ Colourless clear viscous gel of hyaluronic acid of non-animal origin /sterile, apyrogenic, with physiological values of pH/
- ▼ Viscoelastic protector of intercellular matrix of vesical and urethral urothelium



QUALITATIVE COMPOSITION. Sodium hyaluronate. Excipients: Water for injection, Sodium Chloride, Phosphate buffer. **CLASSIFICATION OF THE PRODUCT.** Medical device - sterilized and pyrogen-free - Class IIa. **PACKAGE.** 50ml pre-filled disposable plastic bag which contains 0.16% (80mg/50ml) of hyaluronic acid solution. Each Package contains: 1 plastic bag containing INSTYLAN Sterile solution. The medical device has been sterilized by steam sterilization. **INDICATIONS.** INSTYLAN is intended for irrigation into bladder cavity that provides the formation of a viscous elastic film on the surface of mucous layer to: - protecting it from external effects during various surgeries (ureteroscopy, cystoscopy, transurethral resection of adenoma and radiation therapy of lesser pelvis organs, etc); - protect it from the harmful impact of bladder content (urina) in case of injury or from inflammation of the mucous layer of the bladder, like cystitis. INSTYLAN is intended for irrigation of the bladder when using a urological catheter. The irrigation provides temporary protection and restoration of bladder mucous layer during various surgeries (urethra cystoscopy, radiation therapy, etc). **WARNINGS AND SPECIAL PRECAUTIONS FOR USE.** • Do not use if the solution is not transparent and colorless. • Do not use if the packaging has been opened or is damaged. • The product must be used immediately after opening. • The product is intended for single use. After use, the unused product is no longer sterile. Do not use product residuals; • Do not reuse. Once the product has been used for the first time, any residuals of the product are not suitable for the repeated use as the product is no longer sterile. • Do not resterilize. Repeated sterilization may cause cross-contamination. • Do not freeze. • The product must not be administered orally. **SPECIAL WARNING.** • Do not use the Solution in patients with known hypersensitivity to hyaluronic acid, or those with a history of allergic reactions to any component of the product. • Irrigation into the bladder should be provided by a trained medical specialist in specialized premise with appropriate equipment and aseptic conditions. • Do not inject the solution into blood vessels. • Do not use the product with pregnant or lactating woman, or children. **ADVERSE REACTIONS AND SIDE EFFECTS.** None. **HOW TO USE.** • Check package integrity before use. • Check the expiration date indicated on the bag. Do not use after the expiry date. • Take one of the plastic bags containing INSTYLAN Solution. • Make sure that the bladder of the patient has been previously emptied • Remove the cap • Irrigate the patient's bladder using a urological catheter. **FOR CYSTITIS TREATMENTS:** - It is suggest that the sterile solution INSTYLAN is used weekly for the first month and with less frequency in the following months. The frequency of use of sterile solution INSTYLAN must be determined by the doctor who established the treatment. **SHELF LIFE** 2 years in an intact package. **HOW TO STORE.** Store at temperatures between 5 ° to 30° C (inclusive), away from direct light and heat, in the adequately sealed packaging. The expiry date is applied to the products which are correctly stored in an intact package. **DISPOSAL** The product must be disposed of in accordance with the applicable laws on medical waste