INTRAVESICAL ADMINISTRATION OF HYALURONIC ACID ALONE OR WITH TACROLIMUS AS TREATMENT OF BLADDER PAIN SYNDROME WITH PERIPHERAL SENSITIZATION

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ABSTRACT

Background: Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a severe condition which characterized by symptoms such as suprapubic pain, frequency, reducing of the bladder capacity. The pathogenesis of this syndrome is still unknown, but some attributes were proved last years. There are bladder glycosaminoglycan’s deficiency, non-bacterial inflammation with mast cells activity and peripheral (bladder) sensitization. Hyaluronic acid (HA) instillations widely used for glycosaminoglycan’s replacement therapy. Treatment of bladder sensitization and non-bacterial inflammation usually based on corticosteroids intravesical administration but now we know non-steroid substance with same effects – tacrolimus. We’ve decided to evaluate efficacy of intravesical administration hyaluronic acid alone or with tacrolimus.

Materials and methods: 38 female patients participated in study. Before treatment we evaluated VAS, frequency, O’Leary/Sant questionnaire, IL-8 and NGF level in urine. 19 patients received instillations of hyaluronic acid (0.08% - 50 ml) (“Biocyst”) twice a week for 3 months, 19 patients received instillations of HA with tacrolimus (15 mg/50 ml).

Results: VAS before was 6,8±2,2, frequency was 28,1±7,3, O’Leary/Sant score was 17.3/14.2, IL-8 level was 59,5±20,5 pg/ml (control group - 23,7±2,9 pg/ml), NGF level in urine was 46,8 ± 14,3 pg/ml. After 3-months treatment with HA instillations VAS became 4,3±1,2, frequency 18,2±4,6, O’Leary/Sant score 9.5/8.6, IL-8 level in urine 9,4±2,8 pg/ml, NGF level in urine became 18,4 ± 5,5 pg/ml.

After 3-months treatment with HA plus tacrolimus instillations VAS became 3,1±0,8, frequency 13,5±3,8, O’Leary/Sant score 8.1/7.4, IL-8 level in urine 4,7±0,8 pg/ml, NGF level in urine became 14,2 ± 3,1 pg/ml.

Conclusion: HA intravesical administration is effective option in treatment BPS/IC. Intravesical administration of HA with tacrolimus also showed promised results, better efficacy than HA alone. Further multi-center, placebo-controlled trials needed.

Introduction

BPS/IC is a severe condition with high impact on quality of life. The ESSIC consensus runs that BPS would be diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency.[1] The estimated prevalence of BPS/IC varies considerably, depending upon the criteria used for defining the condition and the data collection methods used.
Epidemiological studies have used a variety of data collection techniques—application of specific diagnostic criteria, physician diagnosis, patient self-report, and surveying for symptoms suggestive of the condition—with a resulting wide range of estimated prevalence. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (based on National Health and Nutrition Examination Survey III [NHANES III]) estimated that 1.2 million women and 82,000 men in the United States have IC/PBS. One study found a prevalence of IC/BPS in the general population of 60 per 100,000, although this is believed to be an underestimate. Indeed, as shown in Figure 1, the prevalence in a managed care population was 197 per 100,000 for women and 41 per 100,000 for men when diagnosed using ICD-9 code.[2,3]

The underlying pathophysiology of this disease is still unknown, but most urologists consider that keystone of BPS/IC is urothelial dysfunction and glycosaminoglycan’s layer failure. The urothelial surface is lined by an impermeable bladder surface mucin composed of sulfonated glycosaminoglycans (GAGs) and glycoproteins.[4] Changes in this surface can cause permeability alterations that allow potassium ions to traverse the urothelium, depolarize sensory and motor nerves, and activate mast cells. This permeability dysfunction is manifested by increased urea absorption and positive potassium sensitivity tests in IC patients[5]. The rationale for the use of “epithelial coating” drugs, such as pentosan polysulfate and intravesical heparin or hyaluronic acid, is their effect on surface epithelial function[6,7,8].

Bladder insult due recurrent bacterial cystitis or primary neurogenic inflammation leads to damage of urothelium and GAG-layer. Irritation of unprotected lamina propria, in turn leads to mast cell activation, increasing NGF level as well as C-fibers density and subsequently bladder peripheral sensitization[9,10,11]. Thereby, bladder became so-called primary pain generator, nerve impulses from bladder activate central nervous system owing to neuroplasticity phenomenon[12].
The excited neurons in PAG-RVM area could activate organs and structures of pelvis and pelvic floor nearby to bladder. It could be reason to hyperalgesia/allodynia of them.

Concomitant diseases of BPS/IC are Irritable Bowel Syndrome (IBS) and Overactive Pelvic Floor (OPF). It means, that colon or pelvic floor muscle become so-called secondary pain generators[13]. Hence, BPS/IC is complex syndrome, contributors of this syndrome are bladder wall, CNS, pelvic floor muscles and pelvic organs[14]. Therefore, treatment should be integrated and expands to all involved organs and systems. However, primary pain generator is bladder (urothelium) and stream of afferent impulses from lamina propria is trigger off vicious circle of BPS/IC.

That is why primary target of treatment is bladder. There are two main goals:
1. Recovery of urothelium’s GAG-layer
2. Reduction of neurogenic inflammation, cytokines an neurotrophins level[15]. Intravesical administration of hyaluronic acid widely used as GAG-replacement therapy and showed its efficacy.
However, HA instillations couldn’t decrease neurotrophins level. Usually, corticosteroids intravesical instillations use with anti-inflammatory purpose, but it has side effects.

New non-steroid anti-inflammatory drug, tacrolimus widely used for last decade. Tacrolimus was prescribed as cream for treatment dermatitis. Also, few articles, devoted intravesical administration of tacrolimus have been published recently.

We decided to evaluate efficacy of intravesical administration of HA (“Biocyst”) alone and HA (“Biocyst”) with tacrolimus.

**Materials and methods:**

38 female patients participated in study. All of them suffered of BPS/IC. ESSIC diagnostic criteria have been used for clarify diagnosis BPS/IC. Patients were evaluated before trial:

1. Visual Analog Scale (VAS) for measurement pain intensity - 6,8±2,2
2. Micturition chart (frequency) - 28,1±7,3
3. O’Leary/Sant score - 17.3/14.2
4. IL-8 level in urine - 59,5±20,5 pg/ml. Also, we evaluated IL-8 level in urine in control group (30 healthy women).
5. NGF level in urine - 46,8 ± 14,3 pg/ml (in control group – 11,4 ± 1,6 pg/ml)

NGF is main neurotrophin, which responsible for C-fibers growth and up regulation, IL-8 is cytokine, responsible for inflammation. That’s why we decided to evaluate their level.

Patients were equally randomized (random numbers) divided into two groups, 19 in each group. Patients in 1st group received instillations of HA (40 mg/50 ml) (“Biocyst”) twice a week for 3 months, 2nd group received HA (40 mg/50 ml) (“Biocyst”) with 15 mg of tacrolimus, dissolved in DMSO. 3 months later both groups have been evaluated.

**Results:**

There weren’t significant side effects, except transitory pain after procedure in few cases.

![Figure 5. VAS before and after treatment. 1 – VAS before treatment; 2 – VAS after treatment in “Biocyst” group; 3 – VAS after treatment in “Biocyst” + tacrolimus group](image)

**1st group:** after 3-months treatment with “Biocyst” instillations VAS became 4,3±1,2, frequency 18,2±4,6, O’Leary/Sant score 9.5/8.6, IL-8 level in urine 9,4±2,8 pg/ml, NGF level in urine became 18,4 ± 5,5 pg/ml.

**2nd group:** after 3-months treatment with “Biocyst” plus tacrolimus instillations VAS became 3,1±0,8, frequency 13,5±3,8, O’Leary/Sant score 8.1/7.4, IL-8 level in urine 4,7±0,8 pg/ml, NGF level in urine became 14,2 ± 3,1 pg/ml.
Figure 6. Frequency before and after treatment. 1 – before treatment (28,1±7,3); 2 – after treatment with “Biocyst” only (18,2±4,6); 3 – after treatment “Biocyst” with tacrolimus (13,5±3,8). There’s statistically significant difference.

O’Leary score

Figure 7. O’Leary score: 1 – before treatment 2 – “Biocyst” group after treatment 3 – “Biocyst” with tacrolimus after treatment

IL-8 level in urine (pg/ml)

Figure 8. IL-8 level in urine: 1 – before treatment 2 – “Biocyst” group after treatment 3 – “Biocyst” with tacrolimus after treatment
**NGF level in urine (pg/ml)**

![NGF level in urine chart]

**Figure 9.**
NGF level in urine:
1 – control group (healthy patients)
2 – before treatment
3 – “Biocyst” group after treatment
4 – “Biocyst” with tacrolimus after treatment

**Conclusions:**
“Biocyst” intravesical administration showed efficacy for treatment BPS/IC. Decreasing of NGF level in urine is evidence of reducing bladder sensitization, IL-8 is evidence of reducing non-bacterial inflammation. However, instillations “Biocyst” with tacrolimus, significantly effective, than “Biocyst” alone. Certainly, we need multicenter trials for confirmation.

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