

## **Intravesical hyaluronic acid instillation in treating recurrent cystitis in women: long term results**

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### **Abstract**

#### **Hypothesis / aims of study**

Recurrent urinary tract infections (RUTIs) are defined in the literature as 3 episodes of urinary tract infections in the last 12 months or two episodes in the last 6 months. UTIs risk factors are genetic and behavioural. In Italy, there are 6 millions UTI per year.

Among the main causes of chronic or relapsing cystitis, there might be an alteration of the transitional epithelium, which is a real protective barrier. Normal bladder epithelium (urothelium) is covered by a protective film formed by glycosaminoglycans (GAG). After a first infectuous event, this barrier gets damaged, and bacteria can penetrate the urothelium, originating inflammatory mechanisms that are the basis of chronic or relapsing cystitis.

Recurrent UTIs are common. RUTI's diagnosis has to be confirmed by a cultural examination of the urine.

A valuable help against cystitis is hyaluronic acid, a second-line treatment following usual antibiotic therapy. It allows for the rebuilding of the internal bladder coating, eliminating inflammation too. In cases of cystitis, the bladder's protective barrier gets altered and bacteria adhere aggressively to the bladder wall.

Hyaluronic acid is a defense tool for the bladder wall, which is attacked by bacteria that adhere to its walls.

It makes the urothelial layer more resistant to bacterial rooting. In cases of recurrent UTI with reinfection, the goal is no longer to try to eradicate the bacterial load, but to reduce symptoms.

Hyaluronic acid works as a defensive barrier since it regulates cellular motility and proliferation, creates a support structure for cellular anchorage, regulates water flux on the cellular surface, prevents the passage of viruses and bacteria to the cell, fixes free radicals (antioxidant action), and regulates the immune and inflammatory response.

Different clinical studies demonstrate that hyaluronic acid is capable of restoring the protective function of the transitional epithelium, contributing significantly to reducing the inflammatory state, reducing UTI's relapse, and resizing and resolving the symptoms.

Hyaluronic acid can be administered intravesically (through a catheter) or orally. Intravesical hyaluronic acid can be used singularly or in association with chondroitin sulfate; it's not painful; it has to be retained in the bladder for at least 30 minutes up to two hours, and it is eliminated with micturition. The instillation is scheduled once a week for 8 weeks, and later maintenance monthly cycles. It has no particular contraindications.

EAU Guidelines show that endovesical instillations of hyaluronic acid and chondroitin sulphate have been used for glycosaminoglycan (GAG) layer replenishment in the treatment of interstitial

cystitis, overactive bladder, radiation cystitis, and for the prevention of rUTI. A review of 27 clinical studies concluded that large-scale trials are urgently needed to assess the benefit of this type of therapy; therefore, no general recommendation is possible at this stage.

### **Study design, materials and methods**

INSTYLAN is composed of Hyaluronic acid, a sterile solution for intravesical irrigation 0,16%, containing in 50 ml, Hyaluronated Sodium 80 mg (high molecular weight, 2 Mda).

In our work, we want to evaluate the ability of INSTYLAN in reducing rUTIs and their symptoms without collateral effects.

We enrolled 24 women, median age 58 years (range 35–75). They had irritative vesical symptoms for at least 8 months and were treated initially with attack therapy and after with cycles of nitrofurantoin or phosphomicin without results. All the patients had ongoing symptoms, with a micturition frequency of at least 8 times per 24 hours.

We evaluated the same parameters in the control group, composed of 20 women, median age 48 (range 34–72) treated with fosfomicin 3 gr once a week for 2 months.

Primary endpoint: reducing UTIs frequency within 3 months.

Secondary endpoints: variation of the micturition frequency's episodes; safety standards; adverse events; post-void residual (PVR) reduction.

We administered 1 instillation per week of INSTYLAN for 8 weeks.

The patients were informed regarding the aims and characteristics of the procedure. They signed an informed consent form.

After emptying the bladder, the patients were put in supine position. We inserted a 14-ch autolubricated catheter for almost all its length. We checked the presence of PVR.

We introduced INSTYLAN in the bladder via catheter.

The patients stayed in supine position for 5 minutes, then they were invited not to urinate for at least 2 hours, and they were invited to go home.

The patients filled out a micturition diary three days before the first and last instillations.

Urinoculture was executed at the beginning and at the end of the therapy.

Adverse events have been evaluated at every visit.

PVR was evaluated via a standard US scan or extemporaneous bladder scan at the first and last visits.

### **Results**

- At the end of the treatment, 20 patients reported satisfaction and clinical improvement; their urinoculture was negative at 3 months. 4 patients underwent UTI relapse (klebsiella and E. coli).
- No hematuria or other systemic effects were observed. No collateral effects were reported (only one case of initial strangury).
- A significative improvement in bladder capacity was reported. GCI was positive in 75% of the cases.

- The control group had a satisfaction in 16 patients.
- At the control at 12 mesi, 16 patients in local therapy had no relapse, 15 patients treated with fosfomicin developed UTI's relapsed.

### **Interpretation of results**

Intravesical instillation of hyaluronic acid repairs the GAG layer on the urothelial surface and therefore prevents bacterial adhesion. A small metanalysis (4 studies, 143 patients) on the efficacy of intravesical hyaluronic acid as possible treatment of UTI's relapse showed promising results.

The authors of a review published in BMJ conclude that, given the evidences, antibiotic prophylaxis remains the gold standard in preventing UTIs' recurrence in women. However, seen the increasing problem of antibiotic resistance, the research of alternative therapies is very active both by patients and doctors.

### **Concluding message**

Albeit on a limited number of patients, our experience with the use of intravesical INSYLAN has been positive, and the patients have been very satisfied. The methodology is simple, and it has substantially no collateral effects.

However, there is a need of a multicentric study versus placebo to get statistically significant data.