

## **Intravesical hyaluronic acid instillation in treating recurrent cystitis in women: preliminar observation**

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### **HYPOTHESIS / AIMS OF STUDY**

Recurrent urinary tract infections (RUTIs) are defined in literature as 3 episodes of urinary tract infections in the last 12 month or as two episodes in the last 6 months. RUTIs 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 which are the basis of chronic or relapsing cystitis. Moreover, a long lasting inflammatory situation modifies sensibility of molecular receptors in nearby nervous tissues, making treatment of eventual long-lasting painful syndrome harder.

Behavioural factors implied with RUTIs comprehend sexual activity, with a higher incidence in women who uses spermicides, frequency of intercourse, use of spermicides, age of first UTI and an history of maternal UTI, which suggests the role of genetical factors and/or long term ambiental exposure.

After menopause risk factors strongly associated with RUTI are vesical prolapse, urinary incontinence and post-voidal residue (PVR).

Different clinical studies demonstrate that hyaluronic acid is capable of restoring the protective function of the transitional epithelium, contributing significantly in reducing inflammatory state, in reducing UTI's relapse and in 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 mantainment 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 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, 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 12 women, median age 54 years (range 35-78). They had irritative vesical symptoms since at least 8 months and were treated initially with attack therapy and after with cycles of nitrofurantoin or fosfomicin without results. All the patients had symptoms ongoing, with a micturition frequency of at least 8 times/24 hrs.

We evaluated the same parameters in the control group, composed of 10 women, median age 48 (range 37-75) treated with fosfomicin 3 g once a week during 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/week of INSTYLAN for 8 weeks.

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

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 a micturition diary 3 days before the first and the last instillation.

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 standard US scan or extemporaneous bladder scan at first and last visit.

## **RESULTS**

At the end of the treatment 10 patients referred satisfaction and clinical improvement, their urinoculture was negative at 3 months. 2 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 significant improvement of bladder capacity was reported.

GCI was positive in 70% of the cases.

## **INTERPRETATION OF RESULTS**

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

Authors of a review published on BMJ conclude that, given the evidences, antibiophylaxis remains the gold standard in preventing UTIs' recurrence in women. However, seen the increasing problem of antibiophage resistance, the research of alternative therapies is

very active both by patients and doctors and, waiting to obtain more evidence on the efficacy of these alternative therapies, in a single patient can be evaluated the use of non antibiomatic prophylactic agent, particularly in those patients who are allergic or don't want to use antibiotics.

### **CONCLUDING MESSAGE**

Recurrent UTIs are common. RUTI's diagnosis has to be confirmed by coltural examination of the urine. Imaging or uretrocystoscopy are not needed as routine investigatios because of their low diagnostic capacity. However these should be performed without delay in atypical cases in the suspect of renal stones, bladder outlet obstruction, interstitial cystitis or urotelial neoplasm.

For RUTIs prevention many approaches have been suggested including non pharmacological therapies such as micturition just after intercourse or blueberry/cranberry juice or antibiotic therapy used on a regular basis or as post coital prophylaxis in sexually active women.

A valuable help against cystitis is hyaluronic acid, a second line treatment following usual antibiotic therapy. It allows to rebuild the internal bladder coating eliminating inflammation too. In case 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 attacked by bacteria who adhere to its walls.

It makes the urothelial layer more resistant to bacterial rooting. In case 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 proliferartion, creates a suppor 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.

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

However there is the need of a multicentric study versus placebo to get satistically significant datas.

### **REFERENCES**

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