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ORIGINAL ARTICLE

Intravesical therapy in recurrent cystitis: a multi-center experience

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Abstract Approximately 20–30 % of women suffer from recurrent cystitis. Recently, the problem of bacterial internalization, especially by *Escherichia coli*, has been significantly emerging as the main cause of recurrent episodes. It is believed that such a process is favored by damage to the urothelial mucous membrane. Concerning this, intravesical therapy with hyaluronic acid alone or in association with chondroitin sulfate was shown to improve urothelium thickness and reduction of bacterial load in the urine. The aim of our study was to assess whether intravesical therapy with hyaluronic acid (HA) and chondroitin sulfate (CS) is more effective than antibiotic therapy in reducing episodes and symptoms of recurrent urinary tract infections. We compared the number of recurring episodes in three groups of patients affected by recurrent urinary tract infections assigned to three different therapeutic regimens: the first group was treated only with HA and CS, the second group with HA and CS associated with fosfomycin, and the third group was treated only with fosfomycin (F). We assessed the number of recurrent episodes for each patient that occurred during a 6- to 12-month follow-up. The results showed 72.7 % of patients in the HA-CS group, 75 % in the fosfomycin + HA-CS group, and only 30.4 % in the fosfomycin group were event free at follow-up. The results were analyzed using the Fisher's exact test. In conclusion, intravesical therapy with hyaluronic acid and chondroitin sulfate is an effective therapeutic approach to treat and prevent episodes of recurrent cystitis.

Keywords Recurrent cystitis · Intravesical therapy · Hyaluronic acid · Chondroitin sulfate · Fosfomycin

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Introduction

Cystitis is a bladder inflammation, either acute or chronic, that can be mild, moderate, or severe and is secondary to a microbiological insult. It is estimated that about 40 % of women experience, at some point in their life, at least one urinary tract infection episode with no complications, which is caused by *Escherichia coli* [1, 2] in 75–90 % of cases.

More importantly, 20–30 % of women suffer from recurrent cystitis; that is, after the first contagion they report two or more episodes of bladder infection within 6 months, or three or more episodes within 12 months, documented by positive urine culture and absence of any functional or structural abnormality of the urinary system. *Escherichia coli* is also the most frequent pathogen for recurrent cystitis, accounting for about 60 % of the cases.

Although it is widely known that individual predisposition resulting from genetic, biological, and behavioral factors [3], as well as inappropriate therapy, favor the onset of recurrent cystitis, recently the problem of bacterial internalization, especially by *Escherichia coli*, has been significantly emerging as the main cause of recurrent

episodes. Internalization is a process through which microorganisms that are naturally extracellular develop the ability to enter the cells and so become protected from the host's defense and antibiotics [4]. It is believed that such a process is favored by morphological damage to the urothelial mucous membrane. The healthy urothelium is indeed coated with a mucopolysaccharide film composed of a variety of elements known as glycosaminoglycans (GAGs), highly hydrophilic molecules that attract water and create a chemical barrier that protects the urothelium. On this basis, as the intravesical administration of some of these GAGs proved to be effective in restoring the urothelial function in interstitial cystitis, several studies have been carried out to evaluate whether such a treatment strategy may also be a practical therapeutic alternative to antibiotics to reduce the episodes of recurrent cystitis [5]. Accordingly, intravesical therapy with hyaluronic acid alone or in association with chondroitin sulfate was shown to benefit urothelial thickness and reduction of the bacterial load in urines.

In agreement with these data, the aim of our study was to assess whether intravesical therapy with hyaluronic acid and chondroitin sulfate is more effective than antibiotic therapy in reducing episodes and symptoms of recurrent urinary tract infections (UTI). We compared the number of recurring episodes in three groups of patients affected by recurrent urinary tract infections assigned to three different therapeutic regimens: the first group was treated only with hyaluronic acid and chondroitin sulfate (HA + CS), the second group with hyaluronic acid and chondroitin sulfate associated with long-term antibiotic therapy with 3 g fosfomycin (HA + CS + F), and the third group was treated only with long-term antibiotic therapy with 3 g fosfomycin (F). We analyzed the efficacy of the three treatment strategies in terms of reduction of recurrent episodes and compared them to establish the best therapeutic approach to reduce both infection recurrence and related symptoms.

Materials and methods

This study was a prospective or retrospective analysis of data from our database. The written patient consent to be enrolled in the study was obtained from all patients. The protocol for the research project has been approved by the Ethics Committee of our University Department, in accordance with the provisions of the Declaration of Helsinki. We recruited from our database 69 patients with an average age of 58.6 years (range, from 53 to 64 years), with a documented history of recurrent cystitis confirmed by at least two episodes of infection without any complication in the previous 6 months or at least three episodes in the previous 12 months. The infection was confirmed by positive urine cultures, which in most cases were positive for *Escherichia coli*.

We excluded from the study patients who did not meet the inclusion criteria, patients older than 70 years, patients with acute infections or already under active treatment, patients with a post-void residual >100 ml, patients with abnormalities of the urinary or genital system, those with fully manifest or suspected diagnosis of stress or urge urinary incontinence, patients suffering from interstitial cystitis or painful bladder syndrome, manifest neoplasm, urinary tract stones, renal insufficiency, or diabetes mellitus, patients using corticosteroids or immunosuppressive agents, spermicidal products or intrauterine devices, or pregnant patients. We have also excluded patients in therapy with systemic or vaginal estrogens to avoid possible biases. Patients who had previously undergone prosthetic surgery were included only after ultrasound investigation to assess the post-void residual, the thickness of the bladder wall, and the correct positioning of the sling inserted to avoid possible biases from postoperative obstructive pathology [6–10].

We performed an objective clinical and anamnestic assessment of the patients, considering medical history, previous urine cultures, and consequent therapies, bladder diary, and the post-void residual through ultrasound scan. Patients were requested to complete a validated questionnaire grading the symptoms (pelvic pain and urgency/frequency: patient symptom scale, PUF scale) to obtain a generic assessment based on the resulting score. The total score range is between 0 and 35. Moreover, we asked the patients to provide a subjective evaluation of their perception of the severity of their symptoms, selecting a grade between 1 and 10, where 0 is the best health state and 10 the worst health state (VAS scale).

To exclude possible organic bladder pathologies and to assess the trophism of the bladder mucosa, we also performed cystoscopy. We excluded interstitial cystitis, according to the NIDDK criteria (National Institute Diabetics, Digestive and Kidney Diseases) [11]. We evaluated the state of inflammation of the bladder mucosa and classified three degrees of inflammation: mild, moderate, and severe. We performed bladder biopsy only in doubtful cases of interstitial cystitis; the latter occurred in only one patient. Patient characteristics are summarized in Table 1.

The patients who complied with the criteria established for the study at the time of first examination were recruited.

To avoid bias, patients were recruited, consecutively, from the database of three different independent investigators (A, B, C): one which is usually administered only antibiotic therapy, one that is usually administered only intravesical therapy, and one which is usually administered a combination of antibiotic + intravesical therapy. All patients showed the same clinical features.

Table 1 Patient characteristics

	Fosfomycin group (no. 23) (Investigator A)	HA-CS group (no. 22) (Investigator B)	Fosfomycin + HA-CS group (no. 24) (Investigator C)
Age, years	57.8	57.4	57.8
Last-year UTI episodes, number	4.58 ± 1.2	4.57 ± 1.3	4.5 ± 1.2
Post-void residual volume evaluation, ml	≤100	≤100	≤100
Total PUF Score	20.5 ± 5.7	21 ± 6.1	20.6 ± 6.8
VAS scale	≥8	≥8	≥8
Cystoscopy	All negative for interstitial cystitis according to NIDDK criteria	All negative for interstitial cystitis according to NIDDK criteria	All negative for interstitial cystitis according to NIDDK criteria
	All with severe mucosal inflammation	All with severe mucosal inflammation	All with severe mucosal inflammation

- *Fosfomycin group* (from the database of Investigator A): 23 patients, average age 58.7 years, treated only by antibiotic prophylaxis with 3 g fosfomycin, one tablet every 10 days for 6 months, as previously reported [12–14].
- *Hyaluronic acid–chondroitin sulfate (HA-CS) group 8* (from the database of Investigator B): 22 patients, average age 58.4 years, treated with 50 ml sterile solution containing 1.6 % hyaluronic acid and 2 % chondroitin sulfate (Ialuril 1; IBSA Farmaceutici, Lodi, Italy). The solution was administered as follows: accurate voiding of the bladder through a 10 Fr. Nelaton catheter, intravesical instillation of the solution once a week for 4 weeks, then once every 15 days for 2 months, and finally once every 30 days for 2 months. After the instillation procedures, patients had to keep the solution in the bladder for at least 2 h, after which they could continue their normal activities. No antibiotic prophylaxis was performed before, during, or after intravesical therapy.
- *Fosfomycin + HA-CS group* (from the database of Investigator C): 24 patients, average age 58.7 years, treated with the same intravesical solution (Ialuril 1; IBSA Farmaceutici), with the same administration schedule as above but associated with long-term antibiotic prophylaxis with 3 g fosfomycin, one tablet every 10 days for 6 months.

For every session of intravesical therapy, each patient was asked to have urinalysis and urine culture 3 days before every instillation. In case of positive results, instillation was delayed until the urine culture was found to be completely negative; the latter occurred in only two patients.

The follow-up included four examinations, at, respectively, 1 month (E1), 3 months (E2), 6 months (E3), and 12 months (E4) after study enrollment. During the recruitment of the patients and in the follow-up examinations we evaluated episodes of recurrent infections confirmed by urinalysis and positive urine culture with associated symptoms (dysuria, pollakiuria, etc.). At E3 and E4 follow-up, we administered the patients the "pelvic pain and urgency/frequency patient symptom scale" (PUF scale) questionnaire and ask them to provide a subjective evaluation of their perception of the gravity of their symptoms and select a subjective grade between 1 and 10, where 0 is the best health state and 10 the worse health state (VAS scale).

In contrast, cytoscopy was performed only at E4.

Results

The aim of our study was to assess the impact of different therapies on the reduction of recurrent episodes of cystitis and to evaluate the related symptoms using a PUF scale and through a subjective assessment of the impact of symptoms (Visual Analogue Scale, VAS). In all our patients the infection was confirmed by positive urine cultures, which in most cases were positive for *Escherichia coli* (97 % of patients). Antibiotic susceptibility testing to ampicillin, amoxicillin/clavulanic acid, cefuroxime, norfloxacin, trimethoprim, ciprofloxacin, cotrimoxazole, nitrofurantoin, and fosfomycin was determined. The results of all tests showed susceptibility to fosfomycin.

Moreover, we assessed whether there had been an improvement in the inflammation of the bladder mucosa through further cystoscopy examinations performed after 12 months. All patients, before beginning any therapeutic programs, had severe inflammation of the bladder mucosa. All cystoscopy examinations were negative for interstitial cystitis and also when a biopsy was taken and analyzed later.

The clinical results were evaluated at 6 and 12 months.

First of all, we considered the number of recurrent episodes for each patient that appeared in the 6-month

follow-up from the beginning of the therapy. The results gathered are as follows:

- Fosfomicyn group (23 patients): 7 patients (30.4 %) did not experience infective episodes and 16 (69.5 %) experienced two or more infective episodes in 6 months.
- HA-CS group (22 patients): 16 patients (72.7 %) did not experience infective episodes but 6 (27.3 %) experienced two or more (2.3 ± 0.2) infective episodes in 6 months.
- Fosfomycin + HA-CS group (24 patients): 18 patients (75 %) did not experience infective episodes but 6 (25 %) experienced two or more (2.5 ± 0.4) infective episodes in 6 months.

As for symptoms evaluation (PUF scale and VAS scale), we noticed a definite improvement only in groups HA-CS and fosfomycin + HA-CS, that is, the group treated with intravesical therapy and the group treated with intravesical therapy and antibiotic prophylaxis. These results obtained are well in line with the percentage of recurring episodes. The latter suggest that the reduction of infections is closely connected not only to urinary symptoms but also to pain and alteration of sexual functions.

It is noteworthy that the results at 6 and 12 months practically coincide in both HA-CS and HA-CS + fosfomycin therapies, whereas the number of patients who experienced recurrent episodes with associated symptoms is higher in the group treated only with fosfomycin. Intravesical therapy with HA and CS appears to be safe and effective in the management of patients with recurrent cystitis. In all patients there were no adverse events or drug interactions with concomitant oral therapies.

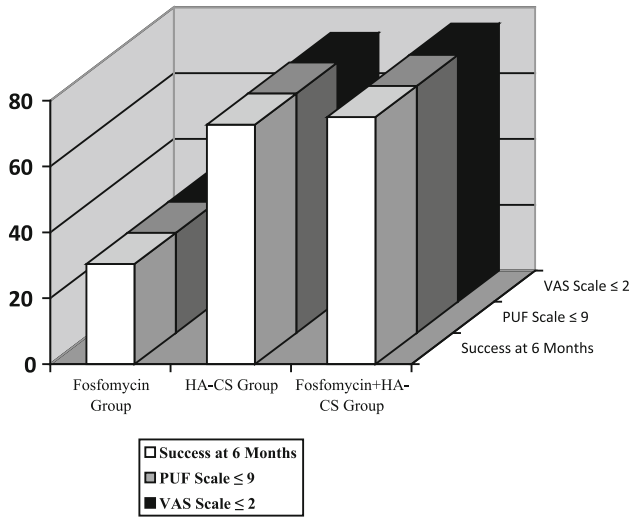

Fig. 1 Results at 6 and 12 months (Fisher's exact test, $p = 0.0029$). *HA-CS* hyaluronic acid and chondroitin sulfate group, *PUF* "pelvic pain and urgency/frequency patient symptom scale," *VAS* Visual Analog Score

The results were analyzed using the Fisher's exact test and proved to be statistically significant for $p = 0.0029$. As for cystoscopy, in the group treated with intravesical therapy, either associated or not with antibiotic therapy, we noticed a reduction of the inflammation at 12 months compared to the respective severe inflammation previously diagnosed. All results are summarized in Fig. 1.

Discussion

For many years, the therapy for recurring cystitis has been based exclusively on the use of antibiotics, sometimes associated with probiotics and cranberry juice [15, 16]. Such a combination is still the therapy protocol most often used in the daily clinical routine. However, although the etiopathogenesis of recurring cystitis is mainly bacterial, this therapy does not reach a significant rate of success in preventing recurrent episodes.

Therefore, it is rational to speculate that other factors may play a key role in the etiology and the mechanisms underlying the chronic phase of this disease. According to the most advocated explanation, the ability of extracellular microorganisms, especially of *Escherichia coli*, to enter the host cells is associated with an alteration of the urothelial mucosa that results in the exposition of adhesion molecules favoring pathogen endurance in the cells and the emission of pro-inflammatory factors. Such a hypothesis supported by many studies that have shown the success of therapies which are innovative in composition and method of administration and effective in reducing the incidence of recurrent infections. The latter therapies specifically act on the reactivation of mucosa junctions, leading to bacterial elimination, thus preventing them from leading to the chronic phase of the disease. These therapies are based on administration of glycosaminoglycans (heparan sulfate, dermatan sulfate, chondroitin sulfate, hyaluronic acid) through direct instillations in the bladder. Glycosaminoglycans are the main components of a healthy urothelium and form a mucopolysaccharide film that works as a chemical barrier and protects the urothelium from exogenous insults. It was previously shown that alterations of this structure constitute the etiopathogenic cause of a number of urinary diseases, among which are interstitial and idiopathic cystitis. However, it has to be noted that such alterations may also be connected to detrusor hyperactivity and stress urinary incontinence. Furthermore, we assume that urothelial dysfunction itself may be one of the factors that favor bacterial colonization as well as the internalization and endurance process of pathogens within epithelial cells. Taking into account the evidence just

summarized and the fact that GAG intravesical instillations improve the symptoms from interstitial cystitis by reestablishing the urothelial barrier, we postulated that this therapy could be an effective therapeutic support to reduce infective episodes in patients experiencing recurring cystitis [17, 18] As a matter of fact, it has been proved that intravesical instillations with HA and CS remarkably reduce recurrent episodes of cystitis and improve the associated symptoms [19]. Many studies have demonstrated that intravesical therapy is more effective than long-term antibiotic therapy in reducing recurrent episodes [20, 21]. In particular, Damiano et al. have shown the effectiveness of intravesical instillations of hyaluronic acid in association with chondroitin sulfate in preventing recurrent infections. Finally, De Vita et al. [22, 23] demonstrated that intravesical therapy with hyaluronic acid and chondroitin sulfate is more effective in reducing recurrent episodes than antibiotic therapy with sulfamethoxazole and trimethoprim.

Our study is squarely rooted within this area of investigation and lends further support to the data recently reported. Indeed, the present retrospective-prospective study shows that the percentages of success in reducing recurrent episodes are higher in patients treated with intravesical therapy or intravesical therapy associated with antibiotic prophylaxis with fosfomycin than in patients treated only with antibiotics. More specifically, intravesical therapy, whether associated or not with fosfomycin, was successful in three fourths of the treated patients whereas antibiotic therapy was successful in less than one third of patients.

It is evident that the local administration of glycosaminoglycans, in particular hyaluronic acid and chondroitin sulfate, in the bladder is a critical factor in reducing urinary recurrent infections. It is also evident that simple intravesical therapy does not require the use of antibiotics and provides better effectiveness on its own when compared to both fosfomycin (as demonstrated by our study) or sulfamethoxazole and trimethoprim (as reported by De Vita et al.) [24]. A growing number of studies indicate that many recurrent urinary tract infections (UTIs) may in effect be relapses caused by the resurgence of intracellular bacterial reservoirs that can persist for many weeks to months within the urothelium [25].

Escherichia coli was the most common uropathogen, followed by *Staphylococcus saprophyticus*, *Enterococcus* species, and *Klebsiella* species. Schmiemann et al. have shown that, in recurrent uncomplicated urinary tract infection, *Escherichia coli* showed higher resistance rates against trimethoprim (25 %) and ciprofloxacin (17 %) but resistance rates for nitrofurantoin (3.4 %) and fosfomycin (0 %) were very low [26].

Antibiotic agents such as beta-lactams, trimethoprim, and cotrimoxazole have been used for the treatment of UTIs. However, the emergence of resistant uropathogens led to a shift to fluoroquinolones, shorter antibiotic regimens, and early switch practices. Yet, resistance to fluoroquinolones has been reported. Additionally, the emergence of uropathogens, mainly *E. coli*, exhibiting high rates of resistance because of the production of extended-spectrum beta-lactamases (ESBLs), is worrisome.

Fosfomycin is an old broad-spectrum bactericidal antibiotic agent that inhibits the synthesis of the bacterial cell. Its pharmacokinetic profile encourages its use for UTIs; the mean peak urinary concentration of an oral single dose of 3 g fosfomycin occurs within 4 h, and concentrations sufficient to inhibit the majority of the urinary pathogens are maintained for 1–2 days. Thus, fosfomycin has been approved as an oral single-dose treatment for acute uncomplicated cystitis. Data from studies evaluating the role of fosfomycin in infections other than UTIs are also encouraging [27].

Yet, nowadays fosfomycin and sulfamethoxazole/trimethoprim are recommended by the American College of Obstetricians and Gynecologists as the first-choice antibiotics in treating urinary recurrent infections [28, 29]. For these reasons, we chose to treat our patients with fosfomycin.

The increased efficacy of intravesical therapy appears to be mainly the result of its capability to prevent the onset of recurrent episodes. In other words, while antibiotics only provide the temporary eradication of the pathogen without reestablishing urothelium functionality and integrity, intravesical therapy acts directly on the urothelium tissue, strengthens its barrier function preventing bacteria from taking root, and therefore acts as a preventive factor for future recurrent infections.

Nevertheless, our study is clearly hypothesis generating. Indeed, it is evident that larger randomized controlled studies are warranted to definitely establish that intravesical therapy with GAGs is actually more effective than antibiotic therapy. Such studies, if eventually positive, would have also the crucial value of significantly arresting the widespread use of antibiotics, the inappropriate use of which has caused not only the development of many drug-resistant bacterial strains but also the increase of morbidity in recurring urinary, intestinal, and vaginal pathologies from its impact on the endogenous flora. As of today, intravesical therapy with hyaluronic acid and chondroitin sulfate is an effective therapeutic approach to treat and prevent episodes of recurrent cystitis. Despite the hypothesis-generating nature of our study and the clear need for further larger and controlled trials, considering the favorable benefit–tolerability ratio demonstrated, we believe that our data, corroborating other similar existing evidence, postulate the need to increase the availability of this

therapy, at least at national excellence centers in urogynaecology.

Conflict of interest The authors report no conflict of interest.

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