



## Original Article

# Is intravesical instillation of hyaluronic acid and chondroitin sulfate useful in preventing recurrent bacterial cystitis? A multicenter case control analysis



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## ARTICLE INFO

## Article history:

Accepted 12 March 2015

## Keywords:

antibiotics  
chondroitin sulfate  
cystitis  
hyaluronic acid

## ABSTRACT

**Objective:** Urinary tract infections (UTIs) are common in the female population and, over a lifetime, about half of women have at least one episode of UTI requiring antibiotic therapy. The aim of the current study was to compare two different strategies for preventing recurrent bacterial cystitis: intravesical instillation of hyaluronic acid (HA) plus chondroitin sulfate (CS), and antibiotic prophylaxis with sulfamethoxazole plus trimethoprim.

**Materials and methods:** This was a retrospective review of two different cohorts of women affected by recurrent bacterial cystitis. Cases (experimental group) were women who received intravesical instillations of a sterile solution of high concentration of HA + CS in 50 mL water with calcium chloride every week during the 1<sup>st</sup> month and then once monthly for 4 months. The control group included women who received traditional therapy for recurrent cystitis based on daily antibiotic prophylaxis using sulfamethoxazole 200 mg plus trimethoprim 40 mg for 6 weeks.

**Results:** Ninety-eight and 76 patients were treated with experimental and control treatments, respectively. At 12 months after treatment, 69 and 109 UTIs were detected in the experimental and control groups, respectively. The proportion of patients free from UTIs was significantly higher in the experimental than in the control group (36.7% vs. 21.0%;  $p = 0.03$ ). Experimental treatment was well tolerated and none of the patients stopped it.

**Conclusion:** The intravesical instillation of HA + CS is more effective than long-term antibiotic prophylaxis for preventing recurrent bacterial cystitis.

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## Introduction

Urinary tract infections (UTIs) are common in the female population [1]. Their recurrence rate is high, reaching 35%, and it generally occurs within 3–6 months [2,3]. Over a lifetime, about

half of women have at least one episode of UTI requiring antibiotic therapy [2]. Currently, as with many other common pathologies, there is no permanent cure for UTI, which often requires a life-long management plan with the goal of maximizing the use of medical treatment [4,5].

UTIs are usually caused by a single pathogen, such as *Escherichia coli* (80%) or *Staphylococcus saprophyticus* (10–15%) [1]. Less frequently, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus* species or *Enterococcus* species can also be found [3]. Acute UTIs are traditionally treated by intermittent or prolonged antibiotic

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therapy, but this management does not appear to give satisfactory results. For this reason, in recent years, the interest in finding new therapeutic and prophylactic drugs has grown significantly. Literature exists on estrogen cream, cranberry juice, and immunostimulatory vaccines but their effects have not yet been proven [6–8].

A new proposal of treatment for UTI consists of hyaluronic acid (HA) instillations [2]. Its use in clinical practice is based on the pathogenic mechanism involved in the development of UTI, and of recurrent infections [2]. In fact, it is likely that the interaction between bacteria and epithelial cells lining the bladder wall plays a significant role [2,9]. In particular, the glycosaminoglycan (GAG) layer lining the transitional bladder epithelium seems to be the most important element implicated in this process. This layer forms a blood–urine barrier, separating the uroepithelium from urine and thereby preventing the adherence of bacteria, crystals and other toxic urinary components [5,10,11]. In contrast, a damaged GAG layer may lead to direct exposure of the uroepithelium to injurious urine components. This leads to an increased risk of bacterial adherence and infection [11]. Therefore, impairment or partial disruption of this layer has been postulated as a causative factor in the development of interstitial cystitis and bladder carcinoma [10,12,13].

HA is a major mucopolysaccharide component of the extracellular matrix of most tissues and constitutes an important proportion of bladder surface GAGs. Chondroitin sulfate (CS) is also a proteoglycan present in the GAG layer and is an important component for bladder mucosal integrity [14,15]. Both HA and CS have been administered orally and/or intravesically in patients with interstitial cystitis to restore integrity of the bladder mucosa [16]. Positive outcomes obtained in the management of interstitial cystitis suggest that a similar therapeutic approach might be beneficial for treating recurrent UTI [2].

Based on these considerations, the present study compared HA + CS intravesical instillation with long-term antibiotic prophylaxis in terms of efficacy and tolerability in women with recurrent UTI.

## Materials and methods

The study protocol was approved by the local Institutional Review Board and written informed consent was obtained from each patient for the use of their data for research purposes.

We retrospectively selected two different cohorts of patients treated for recurrent bacterial cystitis and who received two different therapeutic strategies. We selected them in three different settings in Palermo (Italy): “Villa Sofia-Cervello” Hospital, “P. Giaccone” University Hospital, and “Triolo-Zancla Clinic”. Patient selection was based on documented history of recurrent bacterial cystitis defined, according to the European Association of Urology (EAU) criteria [17], as at least three episodes of uncomplicated cystitis in the past year, with clinical symptoms and/or positive culture for each episode (a positive culture being defined as the isolation of  $>10^3$  colony-forming units of a uropathogen per milliliter of urine).

Cases (experimental group) were women who received intravesical instillations of a sterile solution of high concentration of HA (1.6% w/v – 800 mg/50 mL) and CS (2% w/v – 1 g/50 mL) in 50 mL water with calcium chloride (iAluRil; IBSA Farmaceutici, Lodi, Italy) from January 2011 to January 2012. The instillation was administered slowly using an 8/10 F Nelaton silicon catheter under sterile conditions (after removal of any residual urine). Urine culture was always performed 3 days before the instillation. If a patient developed UTI during the treatment phase, instillations were delayed until urine culture results were negative. After instillation, the patients were asked to retain the instilled solution in the

bladder for  $\geq 2$  hours and then advised to continue their normal habits. The patients received treatment every week during the 1<sup>st</sup> month and then once monthly for 4 months.

The control group included women who received traditional therapy for recurrent cystitis based on long-term antibiotic prophylaxis using sulfamethoxazole 200 mg plus trimethoprim 40 mg (Bactrim; Roche, Milan, Italy) once daily for 6 weeks, during December 2009 to December 2010.

For cases and controls, the exclusion criteria were: previous urinary tract surgery; previous malignancy; diabetes mellitus; radiotherapy; use of prophylactic antibiotic before, during or after bladder instillations; use of any additional drugs and/or supplements; patients with congenital and acquired urogenital abnormalities; and all women who used spermicides or intrauterine devices.

In addition, we included in the final analysis only women who underwent an initial assessment before treatment, including frequency and severity (using an analog visual scale from 0 to 10) of past UTI, the causative pathogens, and clinical and radiological evaluation with ultrasonography and cystoscopy; patients with clinical charts complete for detailed information on adverse events and appearance of any new UTI during treatment; patients who receive complete follow-up visits as commonly performed in our practice for recurrent cystitis (outpatient visits were performed at 1 month, 3 months, 6 months and 12 months after the end of treatment); and patients who underwent outcome assessment addressing UTI status (cystitis recurrence stated on clinical basis confirmed by urine analysis and positive culture).

Statistical analysis was performed with SPSS for Windows version 17.0 (SPSS Inc., Chicago, Illinois, USA). Data were reported as mean and standard deviation. Differences between categorical groups were analyzed by Fisher's exact test and between continuous variables by independent samples *t* test. In all statistical analyses, the level of significance was set at  $p = 0.05$ .

## Results

Ninety-eight and 76 patients were treated in the experimental and control groups, respectively.

There was no difference between the experimental and control groups for age and body mass index (Table 1). During the course of HA + CS treatment, eight episodes of UTI were detected. In these cases, the instillations were delayed until urine culture results were negative.

We excluded 12 patients as follows: three with previous urinary tract surgery, five with diabetes mellitus, one who had radiotherapy, and three with use of additional drugs and/or supplements.

During the 12 months follow up, 69 and 109 episodes of UTI were detected in the experimental and control groups, respectively (Table 2). In both groups, *E. coli* was the most common pathogen in the recurrent episodes, and was identified in 69.3% of cases. The second most common agent was *Klebsiella* (identified in 28.2% of cases). All patients received suitable antibiotic treatment.

**Table 1**  
Demographic characteristics of study patients.

	Experimental group	Control group	<i>p</i> <sup>a</sup>
Patients ( <i>n</i> )	98	76	—
Age, <i>y</i> (mean $\pm$ SD)	36.4 $\pm$ 12.5	39.1 $\pm$ 13.1	0.168
BMI (mean $\pm$ SD)	25.6 $\pm$ 6.7	25.9 $\pm$ 5.8	0.757

BMI = body mass index; SD = standard deviation.

<sup>a</sup> Differences were analyzed by independent samples *t* test.

**Table 2**  
Characteristics of UTIs in both groups after 12 months of follow up.

Group	Experimental	Control	<i>p</i> <sup>a</sup>
Patients ( <i>n</i> )	98	76	—
No. of UTIs	69	109	—
Patients with UTIs, <i>n</i> (%)	62 (63.3)	60 (78.9)	0.03
Patients with 1 recurrence, <i>n</i> (%)	57 (58.2)	24 (31.6)	0.001
Patients with 2 recurrences, <i>n</i> (%)	3 (3.1)	23 (30.3)	< 0.0001
Patients with 3 recurrences, <i>n</i> (%)	2 (2.0)	13 (17.1)	0.001

UTI = urinary tract infection.

<sup>a</sup> Differences were analyzed Fisher's exact test.

Moderate/severe symptoms of UTI, defined arbitrarily as a score higher than seven, were detected in 39.6% of cases (27/69 episodes with positive urine cultures) and 65.2% of cases (71/109 episodes with positive urine cultures) in the experimental and control groups, respectively ( $p = 0.001$ ). The main symptoms were acute dysuria, frequency, urgency, and pelvic pain. Data on the distribution of UTI episodes during follow up are reported in Figure 1.

At 12 months after treatment, 36 (36.7%) and 16 (21.0%) patients in the experimental and control groups, respectively, were free from UTI ( $p = 0.03$ ; Table 2). All women tolerated the HA + CS instillations; in most cases (78%), mild or moderate pain or burning was reported during instillation, but only in 22 cases was anti-inflammatory therapy necessary to relieve the symptoms. None of the patients stopped HA therapy. No serious adverse events were reported during the treatment phase in both groups.

## Discussion

This retrospective analysis demonstrated that HA + CS intravesical instillation is more effective than traditional antibiotic prophylaxis in terms of prevention of UTI recurrence. In addition, it is a feasible and well-accepted treatment. We observed a different ratio of episodes of UTI in the two treatment groups after 12 months of follow up. In particular, the percentage of patients who developed two or three episodes of UTI was mainly found in the group treated with antibiotic therapy. However, the overall percentage of patients with only one episode of UTI was significantly higher in women who received HA + CS intravesical instillations. With reference to the distribution of UTI episodes during follow up, it should be emphasized that, while in the 1<sup>st</sup> month, recurrence was lower with antibiotic therapy, after 12 months of treatment, the number of recurrences was significantly lower in the population treated with HA + CS (Figure 1). Moreover, at 12 months follow up, 36.7% of patients who received instillation of HA + CS were free

from any UTI episodes. It could be the result of long-term repair and consolidation of the urothelial GAG layer. This observation is in agreement with those reported by Damiano et al [2]. Finally, we found a significant difference between the two treatment groups with regard to the onset of symptoms related to the UTI.

The standard treatment for women with recurrent UTI consists of intermittent or prolonged antibiotic therapy (with variable doses and duration of administration), although it is a method with obvious limitations. Persistence of infection and emergence of resistant bacteria are the most common problems [3,11,18]. Changes in the urothelial coating, mainly with a marked reduction in GAGs, can compromise the entire functionality of the urothelium and may contribute to determining different clinical conditions, such as interstitial cystitis, idiopathic detrusor overactivity, and stress urinary incontinence [19]. HA prevents bacterial adherence, repairing the GAG layer of the uroepithelium, while antibiotic therapy aims to eradicate infection.

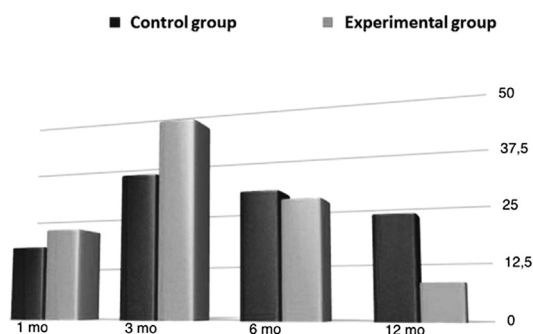
In 2004, Constantinides et al [11] reported the first study on humans regarding the efficacy of GAG layer substitution for preventing recurrent bacterial cystitis. A decrease in the rate of recurrent UTI with HA treatment was shown [11].

Subsequently, Lipovac et al [14] evaluated the efficacy of HA in 20 women with a history of recurrent UTIs. Nine intravesical instillations were administered over 6 months. Thirteen patients (65%) were free from recurrence until the end of the study, and the number of infections per year per patient was significantly reduced from 4.99 to 0.56. The small sample size was a limitation in that study [14]. More recently, in a prospective randomized placebo-controlled study, Damiano et al [2] showed the efficacy of combined HA + CS intravesical instillations in the prevention of recurrent bacterial cystitis. The authors demonstrate that intravesical HA + CS treatment significantly reduced the incidence of UTI with a reduction of absolute risk of 77% of recurrent UTI at 12 months follow up, when compared with patients treated with placebo. In 2012, De Vita and Giordano [20] compared the HA + CS instillation and the antibiotic prophylaxis in the prevention of recurrent UTI in a randomized controlled trial. They observed a significant reduction of the incidence of recurrent cystitis after 12 months of follow up in the group treated with HA + CS instillation. They also underline an improvement of sexual function [20].

In our series, we also used a combined high concentration of HA and CS to significantly reduce the production of proinflammatory cytokines and allow correct repair of the protective layer of the urothelial coating [20]. We compared this treatment to antibiotic therapy and we tried to prove the efficacy of the product administered only for 4 months (as it was proposed by Constantinides et al [11]), to assess if it were feasible to obtain the same or a greater effectiveness than standard antibiotic therapy, using the minimum duration of instillation therapy. Moreover, we reported the data of a large population sample.

A limitation of our study was the retrospective analysis, which could have been a source of bias. We cannot be certain, for example, that patients reported all infections to the clinicians. Moreover, the follow-up period was limited to 12 months. A treatment with intravesical instillations is, obviously, less comfortable than taking an oral antibiotic, although in our series, none of the patients stopped HA therapy and no serious adverse events were reported. In contrast, it is necessary to take possible antibiotic side effects and the impact of increased antimicrobial resistance into consideration [2,20]. Moreover, some women would prefer not to take antimicrobials over an extended period of time [21].

In conclusion, our data, although preliminary, show the validity of this new therapeutic option, which could permit us to avoid repeated and harmful use of antibiotic therapy. Further randomized



**Figure 1.** Distribution of urinary tract infection episodes during follow-up visits.

trials on a larger sample population could also help to confirm the utility of this protocol.

### Conflicts of Interest

The authors have no conflicts of interest relevant to this article.

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