



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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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 1st 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 ≥ 2 hours and then advised to continue their normal habits. The patients received treatment every week during the 1st 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> ^a
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.

^a Differences were analyzed by independent samples *t* test.

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