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ORIGINAL ARTICLE

Effectiveness of intravesical hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: a randomized study

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Abstract
Introduction and hypothesis The glycosaminoglycan hyaluronic acid (HA) protects the urothelium; damage may increase bacterial adherence and infection risk. This study evaluated the effect of intravesical HA in recurrent bacterial cystitis (RBC).
Methods Women with RBC were randomized to intravesical HA 800 mg and chondroitin sulfate (CS) 1 g (IALURIL®, IBSA) in 50 mL of saline solution once weekly for 4 weeks then once every 2 weeks twice more (group 1) or long term antibiotic prophylaxis using sulfamethoxazole 200 mg and trimethoprim 40 mg once weekly for 6 weeks (group 2; control). Evaluations included: cystitis recurrence at 2 and 12 months; subjective pain symptoms (visual analog scale [VAS]); 3 day voiding; sexual function; quality of life (King's Health Questionnaire [KHQ]); frequency symptoms/frequency symptoms (PUF symptom scale); and maximum cystometric capacity (MCC). Means ± standard deviations were reported, with Mann-Whitney test for between-group comparison (significance $P<.05$).
Results Of 28 women (mean age 60±13 y) randomized, 26 completed follow-up (mean follow-up 11.5 mo). Group 1 showed a significant improvement in all evaluations; cystitis recurrence (1±1.2 versus 2.3±1.4, $P=.02$); 3-day voiding (mean 17.8±3.5 vs 24.2±8.3, $P=.04$); symptom VAS (1.6±0.8 vs 7.8±1.6, $P<.001$); PUF score (11.2±2.7 vs 19.6±2.2, $P<.001$), KHQ score (18.4±7.2 vs 47.3±13.6, $P<.001$), and MCC (380±78 vs 229±51 mL, $P<.001$) vs group 2 at 12 mo. No adverse effects were recorded.
Conclusions Intravesical HA and CS in combination significantly reduced cystitis recurrence and improved urinary symptoms, quality of life, and cystometric capacity in RBC patients at 12 mo follow-up versus antibiotic prophylaxis. Study limitations include a small sample and relatively short follow-up.

Keywords Recurrent urinary tract infections · Chondroitin sulfate · Hyaluronic acid · Intravesical instillation · Cystitis

Introduction

Urinary tract infections (UTIs) are very common and affect women much more frequently than men [1–3]. Most acute uncomplicated UTIs are caused by a single pathogen, usually *Escherichia coli* (80 %) or *Staphylococcus saprophyticus* (10 %–15 %) [3]. Less frequent pathogens are *Klebsiella pneumoniae, Enterobacter cloacae, Proteus* species, or *Enterococcus* species. Acute UTIs are traditionally managed by intermittent or prolonged antibiotic therapy [2, 3].

There is a high level of recurrence, and 25 % to 35 % of initial UTI episodes will be followed by a recurrent infection within 3 to 6 months [2, 4]. Therefore, prevention of UTI should be considered for various reasons, especially for patients at risk for UTI.

The conventional prophylaxis consists of intermittent or prolonged antibiotic therapy. However, the prevalence of *E. coli* resistant to antimicrobial agents is increasing; thus, novel non-antibiotic alternative therapies are found to be

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interesting. The reported novel agents include estrogen cream, cranberry juice, and immunostimulatory vaccines such as Uro-Vaxom® (extract of 18 *E. coli* strains), and SolcoUrovac® (10 heat-killed uropathogens), but their effects are not yet proven [5–9].

Many theories had shown that the damage in the glycosaminoglycan layer (GAG) is related to interstitial cystitis physiopathology [10–12]. It has been shown that the GAG layer has a role in protecting the bladder epithelial cells from injury by toxic components of urine, as well as blocking the adhesion of bacteria [13, 14]. Impairment or partial disruption of the GAG layer can lead to the exposure of epithelial cells to toxic or infectious urine components and can increase bacterial adherence and infection [15]. Damage to the layer has been postulated as a causative factor in the development of interstitial cystitis, common UTI, and bladder carcinoma [13, 15, 16].

Hyaluronic acid (HA) is a major mucopolysaccharide component of the extracellular matrix of most tissues and constitutes an important proportion of bladder surface GAGs. Intravesical treatment of interstitial cystitis with HA was shown in different studies to be beneficial with rates varying from 71 % to 30 % [17, 18].

The benefit of HA for women with recurrent UTI has been supported by three recent clinical studies [19–21], in which intravesical instillation of HA has dramatically reduced recurrent UTI. Up to 70 % of patients were recurrence-free at the end of the study follow-up [19–21]. Two of them were observational studies with HA therapy [19, 20] and one was a prospective randomized study with HA and chondroitin sulfate (CS) combination therapy [21]. CS is another natural proteoglycan present in the GAG layer of the bladder epithelium. Like HA, intravesical instillation of this molecule has been proposed as a treatment for patients with interstitial cystitis in order to promote regeneration of GAG in the bladder urothelium.

The aim of this study was to evaluate with a prospective randomized study the beneficial action of intravesical therapy with HA-CS compared with long-term antibiotic prophylaxis in reducing the occurrence for the treatment of recurrent bacterial cystitis (RBC).

Materials and methods

Patients

Eligible patients had a documented history of RBC, defined according to the European Association of Urology (EAU) or the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria [22] as at least three episodes of uncomplicated cystitis with clinical symptoms and/or a positive culture for each episode, defined as the isolation of more than 10^3 colony-forming units of a uropathogen per milliliter of urine.

We excluded patients with congenital and acquired urogenital defects such as interstitial cystitis, urethral duplication, ureterocele, urethral diverticulum, urethro-vaginal fistula, neurogenic dysfunction, and bladder carcinoma. In addition, patients who used spermicides or intrauterine devices, Interventionsor who were pregnant, were also excluded.

Interventions

Patients were randomized according to computer-generated simple randomization into two groups: group 1: intravesical HA-CS treatment or group 2: long-term antibiotic prophylaxis.

Group 1 received intravesical instillations of HA 800 mg and CS 1 g (IALURIL®, IBSA Institut Biochimique SA, Lugano, Switzerland) in 50 mL saline solution once weekly for 4 weeks, then once every 2 weeks twice more. The intravesical instillation was administered in the outpatient clinic using an 8 F Nelaton silicon catheter under sterile conditions, after removing residual urine. Local anesthesia was used with the direct application of xylocaine gel 2 % to the urethra 5 minutes before inserting the catheter. After the instillation, the patients were asked to retain the HA-CS solution in their bladder for more than two hours and then advised to continue their normal everyday habits, including nutrition, smoking, sports, and usual sexual activities.

Group 2 received long-term antibiotic prophylaxis using sulfamethoxazole 200 mg and trimethoprim 40 mg once a week for six weeks [23, 24]. The wash-out period from other previous therapies was at least one month.

Evaluations

All patients were evaluated at baseline and once a week for the first 4 weeks after the initial treatment, and clinical follow-up was performed at 2 and at 12 months after the end of treatment.

Evaluations included:

- Cystitis recurrence assessed by the number of UTI episodes at 2 and 12 months of follow-up (stated on clinical basis –dysuria, pollakiuria- confirmed by complete urine analysis and positive bacterial culture);
- Three-day voiding diary (number of voids in 3 days);
- Subjective urinary pain symptoms, assessed using a visual analog scale (VAS) scored from 0 to 10, at 2 and 12 months of follow-up;
- Pelvic pain and urgency/frequency symptoms assessed using the PUF symptom scale [25];
- Sexual function (frequency, desire, satisfaction and pain) assessed using a questionnaire developed for this study purposes and scored from 0 to 16;

- Impact of urinary incontinence on quality of life (QoL) assessed using the King's Health Questionnaire (KHQ) [26];
- Maximum cystometric capacity (MCC) at baseline and at 12 months' follow-up assessed by cystomanometry [27].
- Every eventual adverse effect was recorded as reported by patients during the follow-up at 2 and 12 months.

Ethics

The study was approved by the hospital's ethics committee and informed consent was obtained before recruitment.

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS 16.0.1, Chicago, Illinois, USA). Continuous variables were reported as mean ± standard deviation. Summary statistics were expressed as mean ± standard deviation. Comparison between quantitative continuous variables was performed using the Mann-Whitney test, a non-parametric test, because of the small sample size. Two-sided *P* values were calculated. Significance level was set at $P=.05$. A $P<.05$ was considered as statistically significant. A post-hoc statistical power of 0.023 was calculated for the two-tailed hypothesis for the primary outcome measure, with an observed effect size (Cohen's d) of 0.137.

Results

Baseline characteristics and patients disposition

Twenty-eight women (mean age 60±13 years) were enrolled and randomized to treatment. Of these, 26 completed the follow-up at 12 months (Fig. 1). The mean follow-up time after completion of therapy was 11.5 months.

Group 1 comprised twelve women of mean age 59± 14 years, while in group 2 there were fourteen women of mean age 61±13 years. Patient characteristics and baseline values are outlined in Table 1. No significant differences were found between treatment groups.

Clinical data

Table 2 summarizes the results of analyzed parameters assessed during the follow-up. Group 1 showed a significant improvement in all considered evaluations at 12 months' follow-up.

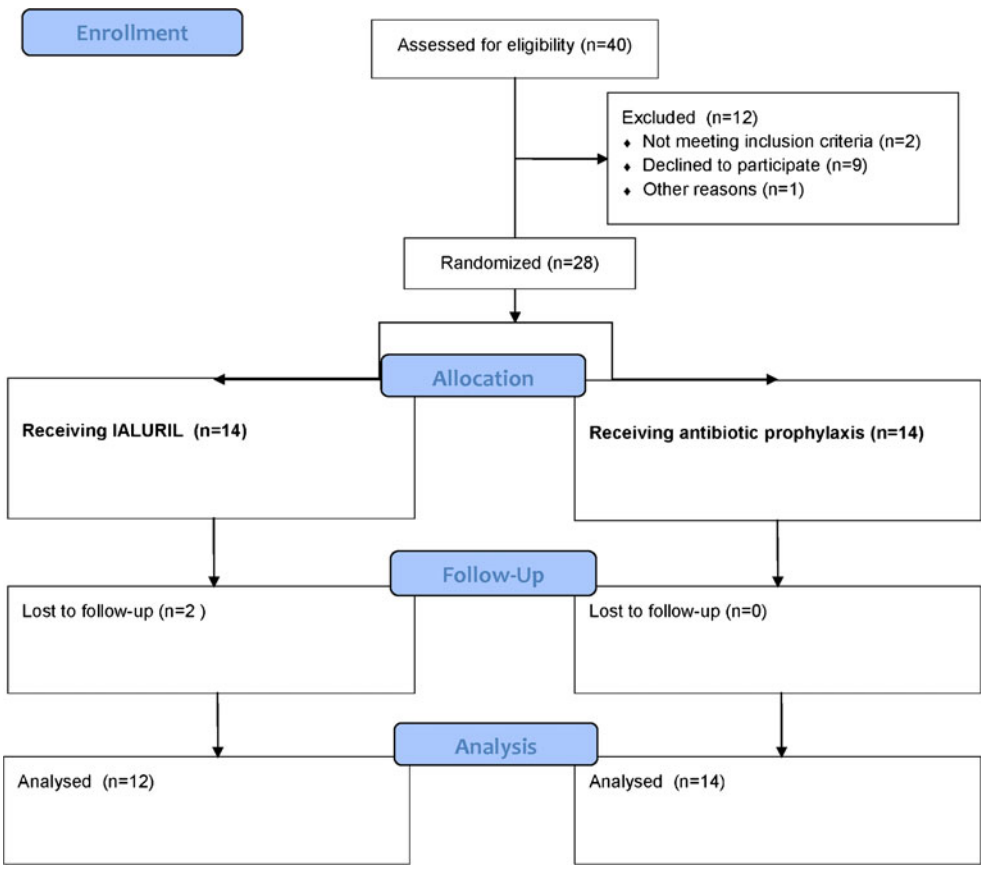

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram

Table 1 Baseline patient characteristics (mean ± SD)

	Group 1 (*N*=12)	Group 2 (*N*=14)	*P* value*
Age (years)	59±14	61±13	0.79
UTI episodes in previous year (n)	6.3±2.9	5.9±1.7	0.69
3 day voids (n)	26.9±11.5	25.2±11.4	0.62
Pain symptom VAS score	8.0±1.9	8.14±1.8	0.87
PUF score	22.7±2.5	22.8±2.2	0.84
Sexual function questionnaire score	6±1.6	4.8±2.0	0.29
King's Health Questionnaire score	51.5±14.5	53.3±13.3	0.54

*Mann-Whitney test

PUF = pelvic pain and urgency/frequency symptoms; SD = standard deviation; UTI = urinary tract infection; VAS = visual analog scale

Comparing group 1 with group 2, there was a reduction of the number of cystitis (UTI) recurrence, which was not significant at 2 months follow-up, but it was significantly reduced in group 1 versus group 2 at 12 months follow-up (1±1.2 versus 2.3±1.4, *P*=.02).

At 12 month follow-up, we observed a significant improvement in 3-day voiding (mean 17.8±3.5 vs 24.2±8.3, *P*=.04); pain symptom VAS (1.6±0.8 vs 7.8±1.6, *P*< .001); PUF symptom scale (11.2±2.7 vs 19.6±2.2, *P*< .001), and KHQ (18.4±7.2 vs 47.3±13.6, *P*< .001). However, these results were not always statistically significant at 2 months' follow-up (Table 2).

In the sexual function questionnaire, we found an overall improvement in sexual function score at 12 months' follow-up (2.4±1.2 vs 6.3±0.8, *P*=.001).

The improvement (increase) in MCC from baseline was significantly greater in group 1 at 12 months follow-up compared with group 2 (380±78 ml vs 229±51 mL, *P*< .001; Table 3 and Figs. 1 and 2).

No adverse effects were recorded.

Discussion

Recurrent UTIs in women are common, result in considerable morbidity and expense, and can be a management problem for physicians. Non-antimicrobial prevention strategies are desirable given the possible adverse effects associated with antimicrobials and the increasing antimicrobial resistance, especially in elderly women.

These data demonstrate that HA-CS is better than weekly antibiotic administration in reducing the incidence of recurrent UTI in women with a history of recurrent UTI, a result consistent with previously published studies [19–21].

HA can block the intercellular adhesion molecule (ICAM)-1 receptor and presumably alleviates the inflammatory processes, reducing inflammatory cytokines [28]. HA targets bacterial adherence to the bladder mucosa, in contrast to antibiotic therapy, which aims to eradicate bacterial infection. HA influences the mechanism of protection against the invasion of *E. coli* and the duration of this effect is about seven days [28]. Thus, repeated instillations are needed to maintain the response [28, 29].

Urothelial dysfunction seems to contribute to different clinical conditions including interstitial cystitis (IC), idiopathic detrusor overactivity (IDO), stress urinary incontinence (SUI), and UTI [30]. The combination of HA and CS bound together by calcium chloride (important for a better interaction with the different GAGs classes and restoration of cell junctions) has been shown to significantly reduce inflammatory cytokines and permit a stabilization and functional improvement of the urothelial apical part (coating) [31, 32].

Table 2 Results of analyzed parameters during follow-up at 2 and 12 months after end of treatment (mean ± SD)

	Group 1 (*N*=12)	Group 2 (*N*=14)	*P* value*
UTI episodes at 2 months (n)	3±1.8	2.9±1.7	0.99
UTI episodes at 12 months (n)	1±1.2	2.3±1.4	.02
3 day voids at 2 months (n)	19.5±4.4	22.8±8.4	0.46
3 day voids at 12 months (n)	17.8±3.5	24.2±8.3	.04
VAS score at 2 months (n)	3.7±1.2	7.1±1.2	<.001
VAS score at 12 months (n)	1.6±0.8	7.8±1.6	<.001
PUF score at 2 months (n)	19.9±2.1	20.6±1.3	0.4
PUF score at 12 months (n)	11.2±2.7	19.6±2.2	<.001
Sexual function questionnaire score at 2 months (n)	4.2±1.6	5.3±1.9	0.16
Sexual function questionnaire score at 12 months (n)	2.4±1.2	6.3±0.8	.001
King's Health Questionnaire at 2 months (n)	23.0±9.4	44.3±14.4	.001
King's Health Questionnaire at 12 months (n)	18.4±7.2	47.3±13.6	<.001

*Mann-Whitney test

PUF = pelvic pain and urgency/frequency symptoms; SD = standard deviation; UTI = urinary tract infection; VAS = visual analog scale

Table 3 Maximum cystometric capacity (MCC)

	Group 1 (N=12)	Group 2 (N=14)	P value*
MCC at baseline	214.2±56.0	224.3±36.9	0.68
MCC at 12 months follow-up	380.0±77.9	229.3±51.4	<.001

*Mann-Whitney test

Efficacious treatment of recurrent cystitis may avoid chronic urine tissue damage, which could lead to interstitial cystitis or painful bladder syndrome [33].

In a previous prospective study, Constandinides et al. [19] found a decrease in the rate of recurrent UTIs with HA treatment. They enrolled 40 women, mean age 35 years, receiving intravesical instillations of HA 40 mg in 50 mL PBS once weekly for 4 weeks and then once monthly for 4 months. The UTI status was assessed over a prospective follow-up of 12.4 months and compared with the rates of UTI before instillation. After HA treatment, 70 % were recurrence free at the end of the follow-up. Side effects were limited to nine patients who reported mild bladder irritation, but no patient interrupted the treatment [19].

Lipovac et al. [20] evaluated the efficacy of HA in 20 women with a history of recurrent UTI (mean age 28 years). Each received nine intravesical instillations of HA 40 mg in 50 mL PBS over 6 months. Thirteen patients (65 %) were recurrence free until the end of the study, and the number of infections per year per patient was reduced from 4.99 to 0.56 ($P<.001$). Small sample size and lack of a control group represented the main study limitations [20].

In a recent prospective, randomized, placebo-controlled study, Damiano et al. [21] showed the efficacy of using combined HA-CS intravesical instillations in the prevention of recurrent bacterial cystitis. They studied 57 women, with mean age 34.8 years, receiving either intravesical instillations of HA-CS ($N=28$) or placebo ($N=29$) once weekly for 4 weeks and then once monthly for 5 months. Follow-up lasted 12 months and 48 % were recurrence free at the end of the follow-up [21].

Despite our smaller patient cohort, we found similar results comparing HA treatment with continuous antibiotic prophylaxis treatment, in a prospective randomized setting. The fact that the mean age of our study population was dramatically higher (60 years versus 28–35 years in previous studies) may explain the higher infection rate the higher urinary pain seen in our control group (group 2) despite long-term antibiotic treatment. In contrast to Constantinides et al. [19], no adverse effects were observed in our study; this might be because of our small group (14 versus 40 patients), and our higher mean age. In addition, we believe that patients in the study conducted by Constantinides et al. had a higher probability of bladder irritation as they received 8 intravesical instillations of HA [19], compared with the 6 instillations of HA-CS in the current study.

We measured patients' quality of life with the KHQ [26], although patients were not incontinent, because it has been chosen as a routine questionnaire in our urogynecological outpatient clinic.

Sexual function also seems to improve after HA-CS treatment, and we measured it because recurrent UTI may produce high pelvic floor muscle tone with consequent dyspareunia [34]

The cost of a course of HA-CS intravesical instillations over a 12-month period (total costs about 1500 Euros) is considerably higher than that of continuous 6-month treatment with nitrofurantoin or quinolone (total costs approximately 1500 Euros versus 30 Euros), which does not take

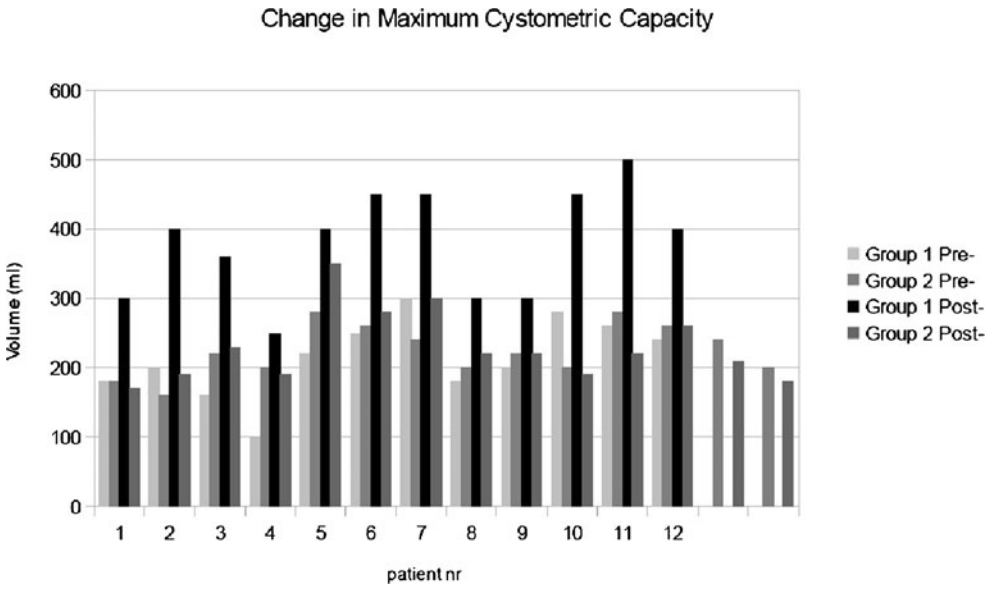

Fig. 2 Maximum cystometric capacity (MCC) in individual patients treated with hyaluronic acid-chondroitin sulfate (group 1) and long-term oral antibiotic prophylaxis (group 2) before treatment (Pre-) and after treatment at 12 months follow-up (Post-)

into consideration additional costs associated with possible antibiotics' side-effects or, particularly, the impact of increased antimicrobial resistance [21]. Indeed, some women do not want to take antimicrobials over an extended period of time [35].

A major limitation is that the study was unblended and all outcome measures included a symptomatic/subjective element; therefore, it is not possible to state whether the results were due to intravesical HA-CS or due to the mode of treatment. However, Damiano et al. [21] performed a placebo-controlled randomized trial, where they observed and concluded that HA-CS intravesical instillations significantly reduced the UTI occurrence rate compared with placebo instillations.

In conclusion, bladder instillation of HA and CS in combination is a feasible treatment option and is well accepted by patients. It reduces the incidence of recurrent lower UTIs significantly, possibly through a protective effect on the GAG layer, and may offer an alternative to the widespread use of antibiotics, which are not always successful or well accepted by patients. However, these results should be interpreted with caution because of the small sample size and the relatively short follow-up period. Further research with larger series of patients and long-term outcomes is needed.

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Conflicts of interest None

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