Effectiveness of intravesical hyaluronic acid with chondroitin sulfate in recurrent bacterial cystitis: 3 years of follow-up.

1Davide De Vita, 2Serena Spartano, 3C. Sciorio
1Department of Obstetrics and Gynaecology, Ospedale S. Maria della Speranza, Battipaglia, Italy
2Hematology Department Università Cattolica del Sacro Cuore, Rome, Italy
3 Department of Obstetrics and Gynaecology, Ospedale S. Maria delle Grazie, Pozzuoli, Naples

Introduction

Urinary tract infections (UTIs) are very common and affect 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 interesting. Many theories had shown that the damage in the glycosaminoglycan layer (GAG) is related to interstitial cystitis physiopathology [5-7]. It has been shown that theGAG 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 [8,9]. 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. Damage to the layer has been postulate as a causative factor in the development of interstitial cystitis, common UTI, and bladder carcinoma [10-12].

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 % [13,14].

The benefit of HA for women with recurrent UTI has been supported by three recent clinical studies [14-15-16], 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. Two of them were observational studies with HA therapy and one was a prospective randomized study with HA and chondroitin sulfate (CS) combination therapy. 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 in reducing the occurrence for the treatment of recurrent bacterial cystitis (RBC).

Materials and methods

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 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 103 colony-forming units of a uropathogen per milliliter of urine (17). 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. 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).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 Evaluations included: cystitis recurrence at 2, 12, 24 and 36 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). Means ± standard deviations were reported, with Mann-Whitney test for between-group comparison (significance $P<.05$). 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.

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 36 months after the end of treatment.

Evaluations included: cystitis recurrence assessed by the number of UTI episodes at 2 and 36 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 24 and 36 months of follow-up; pelvic pain and urgency/frequency symptoms

assessed using the PUF symptom scale; Sexual function (frequency, desire, satisfaction and pain) assessed using a questionnaire developed for this study purposes and scored from 0 to 16.

Results

Of 18 women (mean age 60±13 y) randomized, 12 completed follow-up (mean follow-up 36 mo). All patients showed a significant improvement after 36 months in all evaluations (cystitis recurrence (1±1.2 versus 2.3±1.4, P0.02); 3-day voiding (mean 17.8±3.5 vs 24.2±8.3, P0.04); 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 pretreatment period at 36 mo. No adverse effects were recorded.

At 36 month follow-up, we observed a significant improvement in 3-day voiding (mean 17.8±3.5 vs 24.2±8.3, P0.04); 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) (Table 1). 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, P0.001).

Table 1. Summary of data retrieved from studies on intravescical instillations of hyaluronic acid for recurrent bacterial cystitis. PUF = Pelvic Pain and Urgency/Frequency symptoms; SD = standard deviation; UTI = urinary tract infection; HA = hyaluronic acid group; BT = Before Treatment; * Internal control.

Authors	*Number of patients (HAvsCG)*	*Age (years)*	*Product*	*Hyaluronic acid and Chondroitin sulphate dose*	*Regimen*	*Follow-up*	*UTI-rates per patient-year (HAvsBT)*	*Mean UTI recurrence time (days, HAvsBT)*	*3-day voids (HAvsBT)*	*Total PUF score (HAvsBT)*
De Vita	12	60	IALURIL® (IBSA, Lugano, Switzerland)	50 ml of sterile sodium HA 1.6% and CS 2.0% solution	Once weekly for four weeks, then every 2 weeks 2 times more	36mo.	1.0 vs 2.3	181.5 vs 56.5	17.8 vs 24.2	11.2 vs 19.6

Table 2 Results of analyzed parameters during follow-up 36 months after end of treatment (mean ± SD)

	12 Patients before therapy	12 Patients after therapy (36 mo follow up)	p value
UTI episodes at 36 months (n)	2. 3±1.4	1±1.2	.02
3 day voids at 2 months (n)	22.8±8. 4	19.5±4.4	.0.46
3 day voids at 36 months (n)	24.2±8.3 .	17.8±3.5	.04
VAS score at 2 months (n)	7.1±1.2	3.7±1.2	<.001
VAS score at 36 months (n)	7.8±1.6	1.6±0.8	<.001
PUF score at 2 months (n)	20.6±1.3	19.9±2.1	0.4
PUF score at 36 months (n)	19.6±2.2	11.2±2.7	<.001
Sexual function questionnaire score at 2 months (n)	5.3±1.9	4.2±1.6	0.16
Sexual function questionnaire score at 36 months (n)	6.3±0.8	2.4±1.2	.001
King's Health Questionnaire at 2 months (n)	44.3±14.4	23.0±9.4	. 001
King's Health Questionnaire at 36months (n)	47.3±13.6	18.4±7.2	<.001

*Mann-Whitney test PUF 0 pelvic pain and urgency/ frequency symptoms; SD 0 standard deviation; UTI 0 urinary tract infection; VAS 0 visual analog scale

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 reduce the incidence of recurrent UTI in women with a history of recurrent UTI, a result consistent with previously published studies. HA can block the intercellular adhesion molecule (ICAM)- 1 receptor and presumably alleviates the inflammatory processes, reducing inflammatory cytokines. 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. Thus, repeated instillations are needed tomaintain the response. Urothelial dysfunction seems to contribute to different clinicalconditions including interstitial cystitis (IC), idiopathic detrusor overactivity (IDO), stress urinary incontinence (SUI), and UTI. We measured patients' quality of life with the KHQ, 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. The cost of a course of HA-CS intravesical instillations over a 12-month period (total costs about 1500 Euros).

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.

References

1. Foxman B (2002) Epidemiology of urinary tract infections: incidence, morbidity and economic costs. Am J Med 113:5S–13S
2. Ronald A (2002) The etiology of urinary tract infection: traditional and emerging pathogens. Am J Med 113:14S–19S
3. Chung A, Arianayagam M, Rashid P (2010) Bacterial cystitis in women. Aust Fam Physician 39(5):295–298
4. Foxman B, Gillespie B, Koopman J, Zhang L, Palin K, Tallman P et al (2000) Risk factors for second urinary tract infection among college women. Am J Epidemiol 151:1194–1205
5. Schilling JD, Mulvey MA, Hultgren SJ (2001) Dynamic interactions between host and pathogen during acute urinary tract infections. Urology 57:56–61

6. Reid G (1999) Current scientific understanding of urinary tract infections in women: an overview. World J Urol 17:336–338
7. Gupta K, Stamm WE (1999) Pathogenesis and management of recurrent urinary tract infections in women. World J Urol 17:415–420
8. Poggi MM, Johnstone PAS, Conner RJ (2000) Glycosaminoglycan content of human bladders: a method of analysis using coldcup biopsies. Urol Oncol 5:234–237
9. Morales A, Emerson L, Nickel JC (1997) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology 49:111–113
10. Parsons CL (1997) Epithelial coating techniques in the treatment of interstitial cystitis. Urology 49:100–104
11. Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pflüger H (2003) Comparative assessment of maximal bladder capacity, 0.9% NaCl versus 0.2 M KCl, for diagnosis of interstitial cystitis: prospective controlled study. J Urol 170:807–809
12. Shao Y, Shen ZJ, Rui WB, Zhou WL (2010) Intravesical instillation of hyaluronic acid prolonged the effect of bladder hydrodistention in patients with severe interstitial cystitis. Urology 75 (3):547–550
13. Porru D, Leva F, Parmigiani A, et al (2011) Impact of intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/ interstitial cystitis. Int Urogynecol. doi:10.1007/s00192-011-1546-5
14. Constantinides C, Manousakas T, Nikolopoulos P, Stanitsas A, Haritopoulos K, Giannopoulos A (2004) Prevention of recurrent bacterial cystitis by intravesical administration of hyaluronic acid: a pilot study. BJU Int 93(9):1262–1266
15. Lipovac M, Kurz C, Reithmayr F, Verhoeven HC, Huber JC, Imhof M (2007) Prevention of recurrent bacterial urinary tract infections by intravesical instillation of hyaluronic acid. Int J Gynaecol Obstet 96(3):192–195
16. Damiano R, Quarto G, Bava I et al (2011) Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomized trial. Eur Urol 59(4):645–651.
17. Gillenwater JY, Wein AJ (1987) Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28-29, 1987. J Urol 140(1):203–206