CEOG Clinical and Experimental Obstetrics & Gynecology

Long-term efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis: 36 months' follow-up

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Summary

Purpose of Investigation: To compare the efficacy and safety of intravesical instillation of hyaluronic acid/chondroitin sulfate with conventional long-term antibiotic prophylaxis in women with recurrent bacterial cystitis. *Materials and Methods:* In this analysis of a prospective study, where women with recurrent bacterial cystitis were randomised to intravesical hyaluronic acid 800 mg/chondroitin sulfate 1,000 mg (group 1) or long-term antibiotic prophylaxis (group 2 – control group), patients in group 1 were evaluated 36 months after treatment. Outcomes included cystitis recurrence, subjective pain symptoms based on a visual analogue scale (VAS), three-day voiding, pelvic pain and urgency/frequency symptoms (PUF scale), sexual function questionnaire, quality of life based on King's Health Questionnaire (KHQ), maximum cystometric capacity (MCC), and adverse events. *Results:* Twelve women (mean ± standard deviation 59.3 ± 13.9 years old) underwent follow-up at 36 months after treatment. There were improvements in all efficacy evaluations at 36 months' follow-up, with significantly favourable mean changes from baseline in cystitis frequency (–5.4 episodes/year; $p < 0.001$), three-day voiding (–10.7 voids; $p = 0.002$), urinary VAS (–6.7 points; $p < 0.001$), PUF (–14.2 points; $p < 0.001$), sexual function (–4.3 points; $p < 0.001$) and KHQ (–34.0; $p < 0.001$) scores, and MCC (+131.7; $p < 0.001$). No adverse events were reported. *Conclusions:* Intravesical hyaluronic acid/chondroitin sulfate significantly reduced cystitis recurrence and associated symptoms and was well tolerated in women with recurrent bacterial cystitis at 36 months' after treatment.

Key words: Chondroitin sulfate; Hyaluronic acid; Intravesical instillation; Recurrent bacterial cystitis; Recurrent urinary tract infection

Introduction

Urinary tract infections (UTIs) are characterised by dysuria, urinary frequency and urgency, haematuria, and suprapubic pain [1, 2]. UTIs are the most frequently occurring type of bacterial infection, and affect significantly more women than men [3]. Recurrent UTIs are also common, occurring in 25% of patients within six months of the initial UTI episode [4, 5]. Over a lifetime, up to 5% of women will experience recurrent UTIs [5].

Patients with a history of recurrent UTIs have an increased risk of irritative urinary symptoms and secondary provoked vestibulodynia or sexual pain, even in the absence of an active infection [5, 6]. Therefore, recurrent UTIs can have a significant impact on patient quality of life [3] and strategies for prevention of recurrent UTI should be considered [7].

Most uncomplicated UTIs are caused by colonisation with *Escherichia coli*, although other species of Enterobacteriaceae are occasionally associated with UTIs, including *Staphylococcus saprophyticus*, *Klebsiella pneumoniae* or *Proteus mirabilis* [5, 8].

In conjunction with behavioural modifications (e.g. avoidance of risk factors), conventional prophylaxis for recurrent UTIs usually includes short- or long-term treatment with antibiotics [9]. Several non-antimicrobial treatments may also prevent recurrent UTIs, including vaginal estrogen replacement [10, 11], immunoactive prophylaxis, *Lactobacillus* strains of probiotics, and cranberry products, although there is limited evidence to support their use [9].

Another non-antimicrobial therapy for recurrent UTI consists of intravesical instillations of hyaluronic acid and chondroitin sulfate. Hyaluronic acid (a major mucopolysaccharide) and chondroitin sulfate (a proteoglycan) are both important components of the protective glycosaminoglycan layer that lines the transitional bladder epithelium [12, 13]. Damage to the glycosaminoglycan layer, which may lead to direct exposure of the bladder epithelium to the potentially injurious substances in the urine, is thought to increase the risk of bacterial adherence and in-

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Revised manuscript accepted for publication November 8, 2017

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fection, and has been proposed to be a causative factor for UTIs, interstitial cystitis, and bladder carcinoma [12-14]. In clinical studies, intravesical administration of hyaluronic acid, either alone or in combination with chondroitin sulfate, was shown to significantly reduce UTI recurrence and improve symptoms among women with recurrent UTIs [14-17].

De Vita *et al.* [18], in a prospective, randomised study, compared the efficacy and safety of intravesical instillation of hyaluronic acid/chondroitin sulfate with conventional long-term antibiotic prophylaxis in women with recurrent bacterial cystitis, a type of UTI [18]. The objective of this current analysis was to evaluate the long-term effects of intravesical hyaluronic acid/chondroitin sulfate in these patients at 36 months after treatment.

Materials and Methods

The design and methods of this study have been previously described in detail [18]. Briefly, patients with a documented history of recurrent bacterial cystitis (as defined by the European Association of Urology [9] or the National Institute of Diabetes and Digestive and Kidney Diseases [19]) were eligible for inclusion. Patients were excluded if they had urogenital defects (congenital or acquired), used spermicides or intrauterine devices, or were pregnant. This study was approved by the Hospital's Ethics Committee (N. 128/2014), and informed consent was obtained before recruitment.

Initially, patients were randomly assigned to two treatment groups by computer-generated simple randomisation. All patients underwent a washout period of at least one month before starting treatment. In treatment group 1, patients received intravesical instillations of hyaluronic acid 800 mg/chondroitin sulfate 1,000 mg in 50 mL saline solution once a week for four weeks, followed by once every two weeks for a further two doses. Intravesical administration was conducted via an 8F Nelaton silicon catheter under sterile conditions in an outpatient clinic. After removal of residual urine, the catheter was inserted under local anaesthesia (topical xylocaine 2% gel). Following each instillation, patients were instructed to retain the solution in their bladder for more than two hours before continuing with normal daily activities. Patients in treatment group 2 (control group) received long-term antibiotic prophylaxis with oral sulfamethoxazole 200 mg/trimethoprim 40 mg once a week for six weeks.

Patient evaluations were conducted at baseline and once weekly for four weeks after the start of treatment, and follow-up visits were performed at two and 12 months after the end of treatment. For the current analysis, patients in treatment group 1 were evaluated at 12 and 36 months after the end of treatment.

The following outcomes were evaluated at baseline and at the 12- and 36-month follow-up visits: cystitis frequency (number of UTI episodes per year based on clinical symptoms and confirmed by urinalysis and positive bacterial culture), three-day voiding diary (number of voids in three days), subjective urinary pain symptoms, based on a visual analogue scale (VAS) [score range 0–10], pelvic pain and urgency/frequency (PUF) symptom scale (score range 0–35), sexual function questionnaire developed for this study, assessing frequency, desire, satisfaction, and pain (score range 0–16), the King's Health Questionnaire (KHQ) single-item domain for impact of urinary incontinence on quality of life (score range 0–100), maximum cystometric capacity (MCC), evaluated using cystomanometry (at baseline and at the 36-month visit), and all patient-reported adverse events.

Statistical analyses were conducted using SPSS Statistics, version 20.0. Continuous variables and summary statistics were reported as mean ± standard deviation.

For the current analysis, patients in treatment group 1 were evaluated at 12 and 36 months at the end of treatment. In fact, the two smaller groups of group 1 (follow -up for 12 months and follow -up for 36 months) participated in the statistical analysis.

Analysis of the differences between quantitative continuous variables at baseline and after 12 and 36 months' follow-up were performed using the paired samples two-sided *t*-test. A p-value of < 0.05 was considered to be statistically significant.

Results

As previously described, this study enrolled 28 women with recurrent bacterial cystitis who were randomised to treatment [18]. Twenty-six women completed follow-up at 12 months after treatment with intravesical hyaluronic acid/chondroitin sulfate (n=12) or long-term antibiotic prophylaxis (n=14). In treatment group 1, follow-up at 36 months after the end of treatment was completed for 12 women (mean age 59.3 ± 13.9 years). Two women not completed follow-up at 12 months and were not ranked in any group.

At 12 and 36 months' follow-up, 12 women who had received intravesical hyaluronic acid/chondroitin sulfate for recurrent bacterial cystitis had significant improvements from baseline in all efficacy evaluations (Table 1). Significant mean reductions from baseline were observed at 36 months after treatment in cystitis frequency (–5.4 episodes/year; $p < 0.001$), three-day voiding (–10.7 voids; $p = 0.002$) and urinary pain VAS scores (–6.7 points; $p < 0.001$), and mean patient scores on the PUF (–14.2 points) and sexual function (–4.3 points) questionnaires and the KHQ domain for the impact of urinary incontinence (–34.0 points) were significantly decreased (improved) ($p < 0.001$ for each). Mean MCC values were also significantly higher (improved) at 36 months' follow-up, with a mean increase from baseline of 131.7 mL ($p < 0.001$) (Table 1). There were no reported adverse events at 36 months' follow-up.

Discussion

In this prospective study, intravesical hyaluronic acid/chondroitin sulfate provided sustained improvements from baseline in bacterial cystitis-related symptoms in women with recurrent bacterial cystitis for up to 36 months after treatment, including cystitis frequency, number of voids, urinary pain symptoms and PUF, sexual function, and quality of life questionnaires. The results of this analysis are consistent with those observed at 12 months after treatment [18].

The findings of the current study are consistent with data from previous prospective studies [14-17] of hyaluronic acid (alone or in combination with chondroitin sulfate) and

Table 1. — *Efficacy of intravesical hyaluronic acid/chondroitin sulfate in 12 women with recurrent bacterial cystitis after 12 and 36 months' follow-up.*

Outcome	Baseline, mean ± SD	At 12-month visit		At 36-month visit	
		Mean ± SD value	Change from baseline, mean (95% CI)	Mean ± SD value	Change from baseline, mean (95% CI)
Cystitis frequency, no. of episodes/year	6.3 ± 2.87	1.0 ± 1.21	–5.33 (–6.85 to –3.82)**	0.9 ± 0.52	–5.42 (–7.18 to –3.65)**
3-day voiding diary, no. of voids/3 days	26.9 ± 11.52	17.8 ± 3.49	–9.08 (–14.78 to –3.39)*	16.3 ± 3.02	–10.67 (–16.37 to –4.96)*
Urinary pain, VAS score	8.0 ± 1.86	1.6 ±0.79	–6.42 (–7.55 to –5.29)**	1.3 ± 0.49	–6.67 (–7.92 to –5.42)**
PUF score	24.2 ± 3.13	10.6 ± 1.62	–13.58 (–15.69 to –11.48)**	10.0 ± 1.41	–14.17 (–16.43 to –11.90)**
Sexual function questionnaire score	6.0 ± 1.58	2.4 ± 1.24	–3.56 (–4.34 to –2.78)**	1.7 ± 0.87	–4.33 (–5.19 to –3.47)**
Impact of incontinence on QOL, KHQ score	51.5 ± 14.53	18.4 ± 7.24	–33.08 (–42.58 to –23.59)**	17.5 ± 6.14	–34.00 (–43.32 to –24.68)**
MCC, mL	214.2 ± 56.0	380.0 ± 77.9		345.8 ± 65.57	+131.67 (108.87–154.47)**

*CI: confidence interval; KHQ: King's Health Questionnaire; MCC: maximum cystometric capacity; PUF: pelvic pain and urgency/frequency questionnaire; QOL: quality of life; SD: standard deviation; VAS: visual analogue scale. *$p < 0.01$, **$p \leq 0.001$ vs. baseline.*

retrospective studies [5, 19, 20] of hyaluronic acid/chondroitin sulphate in women with recurrent bacterial cystitis.

In the present study, mean MCC values were significantly improved compared with baseline at 36 months after hyaluronic acid/chondroitin sulfate treatment. These findings are also consistent with observations at 12 months' follow-up, where improvements in MCC significantly favoured intravesical hyaluronic acid/chondroitin sulfate over long-term oral antibiotic prophylaxis (380.0 mL *vs.* 229.3 mL; $p < 0.001$) [18].

In a case-control study by Arya *et al.* [6], women with a history of recurrent UTI had significantly lower MCC values than controls, and there was a significant correlation between MCC and maximum voided volume. These data suggest that improvements in MCC with hyaluronic acid/chondroitin sulfate treatment in women with recurrent bacterial cystitis may contribute to the observed reduction in urinary urgency and frequency symptoms.

The exact mechanisms by which hyaluronic acid/chondroitin sulfate provides protective effects against recurrent bacterial cystitis are not fully understood. In addition to the prevention of bacterial adherence through restoration of the urothelial glycosaminoglycan layer, hyaluronic acid is thought to decrease bladder inflammation via blockade of intercellular adhesion molecule-1 receptors [21]. Hyaluronic acid was also found to significantly decrease the rate of *E. coli* growth and provide protective effects to the urinary bladder epithelium in a rat UTI model [7]. Effective non-antimicrobial treatment of recurrent bacterial cystitis with glycosaminoglycan molecules such as hyaluronic acid and chondroitin sulfate may also reduce the risk of interstitial cystitis/bladder pain syndrome, which has been linked to chronic bacterial infections and disruption of the glycosaminoglycan layer [22].

In two previous prospective [14, 15], non-randomised studies, intravesical hyaluronic acid once weekly for four weeks followed by once monthly for up to five months was associated with significant reductions in UTI rates in women with a history of recurrent bacterial cystitis. These studies enrolled 40 women (mean age 35 years) [14] or 20 women (mean age 27.7 years) [15] with recurrent bacterial cystitis, and outcome assessments were conducted over a mean of 12.4 months or 47.6 weeks, respectively. A subsequent prospective study by Ząbkowski *et al.* [17] showed 75% reduction in frequent urination without urgency at day and at night in 69% of women with recurrent bacterial cystitis after treatment with intravesical hyaluronic acid once weekly for six weeks followed by once monthly for eight months. In this study, 23 women (mean age 35 years) with a history of recurrent bacterial cystitis were enrolled and followed for eight months after treatment.

In a randomised, placebo-controlled study of 57 women with recurrent UTI (mean age 34.8 years), intravesical instillations of hyaluronic acid/chondroitin sulfate over six months (once weekly for four weeks then once monthly for five months) provided a significant reduction in the number of UTI episodes over 12 months compared with placebo [16]. Although the mean number of voids over three days was similar between the treatment groups, hyaluronic acid/chondroitin sulfate was associated with significant improvements in PUF scale and quality of life questionnaire scores. After 12 months' follow-up, significantly more patients were free from UTI recurrence in the hyaluronic acid/chondroitin sulfate than the placebo group (48% *vs.* 0%; $p < 0.001$) [16].

Data from a meta-analysis that included three of the previous prospective studies [14-16] and the 12-month follow-up results of the current study [18] also supports the use of hyaluronic acid in women with recurrent bacterial cystitis [23]. In this analysis, hyaluronic acid (alone or in combination with chondroitin sulfate) was associated with a significantly decreased rate of UTI per patient-year (mean

difference [MD] –3.41, 95% CI –4.33 to –2.49; $p < 0.00001$) and a significantly prolonged time to UTI recurrence (MD 187.35 days, 95% CI 94.33–280.37; $p < 0.0001$) [23]. The main differences between the current study and the previous prospective trials are the smaller number of patients treated with hyaluronic acid/chondroitin sulfate (12 *vs.* 20–40) and the higher mean patient age (59.2 *vs.* 27.7–35 years).

The effectiveness of hyaluronic acid/chondroitin sulfate in the real-world treatment of women with recurrent UTIs has also been assessed in two retrospective multicentre studies [5, 20]. In a study by Cicione *et al.* [5] (n=157; mean age 54.2 years), six months' treatment with intravesical hyaluronic acid/chondroitin sulfate was associated with a significant decrease in UTI episodes and a significant increase in time to UTI recurrence at 12 months after treatment. According to a study by Ciani *et al.* [20] (mean age 53 years), hyaluronic acid/chondroitin sulfate (n=181) appeared to reduce the risk of bacteriologically confirmed recurrence compared with standard of care treatment (n=95) over 12 months' follow-up (adjusted odds ratio 0.51, 95% CI 0.27–0.96), although the total number of recurrences (adjusted incidence rate ratio 0.99, 95% CI 0.69–1.43) and time to first recurrence (hazard ratio 0.99, 95% CI 0.61–1.61) did not significantly differ between groups.

In the present study, intravesical hyaluronic acid/chondroitin sulfate was well tolerated, with no adverse events reported at 36 months' follow-up. By comparison, in the randomised placebo-controlled study [16], three women (11.1%) reported moderate storage urinary symptoms in the absence of infection with hyaluronic acid/chondroitin sulfate (*vs.* none with placebo), and in the prospective study by Constantinides *et al.* [14], nine women (23%) experienced mild bladder irritation within six hours of the hyaluronic acid instillation. The absence of adverse events in the current study may be due to the smaller patient population; however, it should also be noted that patients in the previous studies received eight [14] or nine [16] instillations of hyaluronic acid or hyaluronic acid/chondroitin sulfate, respectively, while patients in the current study received six intravesical instillations of the study drug. Nevertheless, the placebo-controlled trial by Dami*ano et al.* [16] also concluded that intravesical hyaluronic acid/chondroitin sulfate significantly decreased UTI recurrence compared with placebo in women with a history of recurrent UTIs.

The total cost of intravesical hyaluronic acid/chondroitin sulfate therapy over one year (approximately € 1,500) is much higher than a six-month course of antibiotic prophylaxis [16, 20]. However, these costs do not take into account the increased risk of antimicrobial resistance with long-term antibiotic therapy [16]. Furthermore, antibiotic therapy over an extended period of time is not accepted by some women [24]. Bruyère *et al.* [25] evaluated annual primary incidence of UTI and annual risk of recurrence at 5.3% and 30%, respectively. Greater water intake induced a risk reduction of 45% and 33% for the general and recurrent populations, respectively. The average total healthcare cost of a single UTI episode was € 1.074; for a population of 65 million, UTI management represented a cost of €3,700 million for payers. With adequate water intake, the model indicated a potential cost savings of € 2,288 million annually, by preventing 27 million UTI episodes. At the individual level, the potential cost savings was approximately €2,915. However, cost-effectiveness analyses on the use of hyaluronic acid/chondroitin sulfate in recurrent bacterial cystitis are warranted.

The main limitations of the current study were its non-blinded design, small patient population, and subjective outcome measures. As such, it is difficult to confirm whether the observed results were due to the study drug or the mode of treatment.

In conclusion, the majority of recurrent bacterial cystitis are reinfection from extraurinary sources such as the rectum or vagina. E. coli invades urothelial cells and forms quiescent intracellular bacterial reservoirs (QIRS) that could be a source for bacterial persistence and recurrent bacterial cystitis [26]. Thus, intravesical instillation of hyaluronic acid/chondroitin sulfate is an effective and well-tolerated non-antimicrobial treatment for patients with recurrent bacterial cystitis that provides sustained clinical benefits for up to 36 months after treatment.

Acknowledgments

The authors thank Sarah Greig, PhD, of Springer Healthcare Communications, for medical writing assistance in preparing the first draft of this manuscript. This assistance was founded by IBSA Farmaceutici Italia S.r.l., Lodi, Italy.

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