

The role of hyaluronic acid in the management of uncomplicated recurrent female urinary tract infections: literature review and practical experience

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Abstract

Aim: To assess the efficacy and safety of intravesical hyaluronic acid (HA) in the management of female patients with recurrent urinary tract infections (UTIs) in our hospital. Also to perform a literature review about the use of Glycosaminoglycan (GAGs) such as hyaluronic acid (HA) and chondroitin sulphate (CS) in the management of female recurrent UTI and compare our findings to the published evidence available.

Method: We performed a literature review of studies using HA or CS for the management of recurrent UTIs. We retrospectively reviewed the outcome of 22 female patients who were treated at our district general hospital for recurrent UTIs refractory to first line management and compared our experience of using this treatment to the recently published literature.

Results: Literature review showed growing evidence for the use of intravesical HA and HA-CS for the prevention of female recurrent UTIs including three recently published prospective randomised controlled trials (RCTs). These studies show a reduction in UTIs by over 70% in comparison to placebo and that intravesical treatment is more effective than low dose antibiotic prophylaxis. In our experience, intravesical HA was an effective second line treatment for females with recurrent UTIs. Of 22 patients with recurrent UTIs (aged 17 - 72 years), 64% (14 patients) remained recurrence free one year after treatment. In our experience, this treatment was tolerated well by the patients with minimal side effects.

Conclusion: HA offers an effective management option for female patients with recurrent UTIs. It is a safe and effective second line treatment for female patients with recurrent urinary tract infections that may be refractory to first line management strategies.

Keywords

Recurrent urinary tract infection, hyaluronic acid, GAG, prevention, intravesical treatment

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Introduction

Up to half the population of women will suffer a urinary tract infection (UTI) within their lifetime, of which 25–35% will have a recurrent infection within 3–6 months.^{1,2} UTIs are therefore one of the commonest bacterial infections, and although associated with minimal morbidity they have a significant effect on quality of life and incur considerable financial costs.³ In 1995 the annual direct and indirect costs incurred as a consequence of community-acquired UTIs in

the USA amounted to \$1.6 billion and accounted for 15% of all antibiotics prescribed in the USA.^{3,4}

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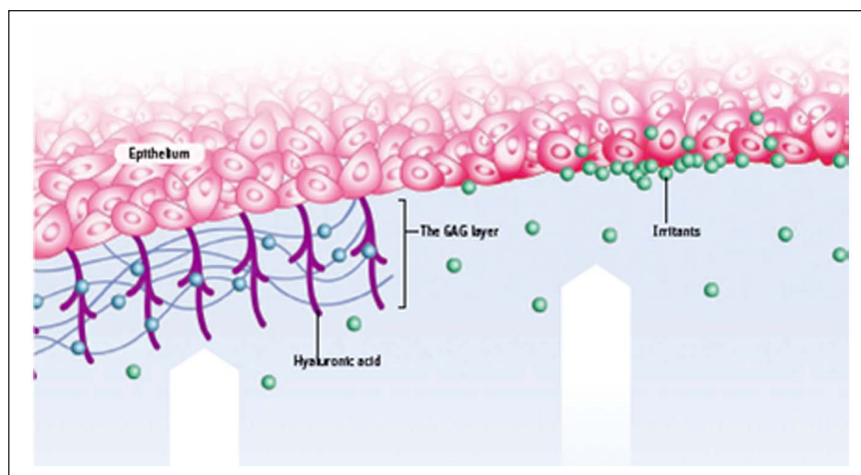


Figure 1. Effect of HA to restore the GAG layer. (Reproduced with permission from Teva UK Limited).
HA: hyaluronic acid; GAG: glycosaminoglycan.

The pathogenesis of UTIs is complex and depends on the balance between bacterial virulence and host response. Several studies have highlighted the importance of the glycosaminoglycan (GAG) layer in the pathogenesis of urinary infections.⁵

The transitional epithelium of the bladder is lined by a GAG layer composed of glycoproteins and proteoglycans which form a hydrophilic physico-chemical barrier against solutes, bacteria and toxic substances within the urine.^{1,6} The GAG layer is produced by bladder urothelial cells and includes non-sulphated GAGs such as hyaluronic acid (HA) as well as sulphated GAGs such as chondroitin sulphate (CS).^{5,6}

Damage to the GAG layer has been implicated in the pathogenesis of several disease processes including interstitial cystitis/bladder pain syndrome (IC/BPS), radiation cystitis and recurrent UTIs. The GAG layer plays a key role in the prevention of UTIs by preventing bacterial adherence to the bladder wall but it is also important in protecting the uroepithelium from exposure to urinary toxins.^{6,7} Even in the absence of infection (such as in IC/BPS) direct exposure of the urothelium to urinary toxins can result in C-fibre activation, smooth muscle contraction and mast cell activation resulting in symptoms of allodynia, urgency and frequency.^{5,6}

Several treatments have been developed to try and replenish the GAG layer including intravesical instillations (e.g. HA, CS and combinations of the two) as well as oral pentosan polysulphate (Figure 1). Initial research focussed on IC/BPS and studies have subsequently demonstrated that intravesical HA, CS and pentosan polysulphate sodium can all be effective treatments.^{2,5,8}

More recently, investigators have assessed whether these treatment strategies used to replenish the GAG layer in patients with IC/PBS may be effective in the prevention of recurrent UTIs.

Methods

In our department approximately 150 patients are diagnosed every year with UTIs and are assessed in the multidisciplinary urology clinic by a consultant urologist and continence nurse specialist. We undertook a retrospective review of all female patients with recurrent UTIs (EAU definition – see Box 1) who failed standard treatment and offered a course of HA instillation between December 2009 and June 2011. All notes were reviewed along with mid-stream urine microscopy and culture results. We excluded patients who did not have positive urine culture.

Box 1. A recurrent UTI as defined by the European Association of Urology is three or more uncomplicated infections documented by urine culture with greater than 10^3 colony-forming units/ml in the last 12 months³

Patients with apparent UTI symptoms but who had negative nitrates and leucocytes, and no bacterial growth were excluded. These patients did not fit our criteria of recurrent UTIs, which depended on positive cultures for identifying our patients.

All patients were assessed by urine dipstick, mid-stream urine (MSU) for culture and sensitivity and ultrasound of the kidneys, ureters and bladder (in view of recurrent UTIs). All patients were initially offered lifestyle and fluid management advice as well as, depending on clinical assessment, additional management strategies such as: three- to six-month low-dose daily prophylactic antibiotics, six-month course of local vaginal oestrogen cream (for atrophic vaginitis) and cystoscopy and urethral dilation (for persistently high post-void residual volumes) (Figure 2). Twenty-two patients were refractory to these initial management strategies, therefore were offered a course of intravesical HA.

Intravesical HA was administered weekly for four weeks and then monthly for two months (total six doses, according

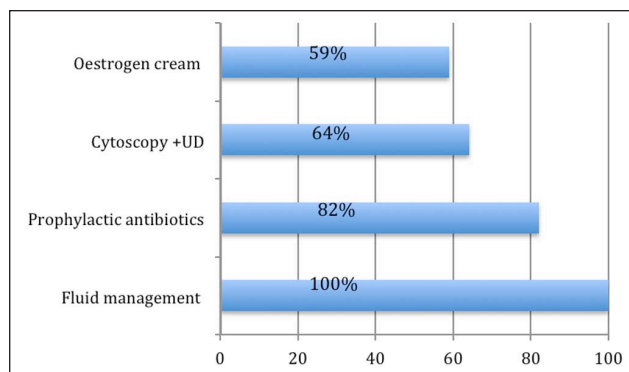


Figure 2. Treatment received prior to hyaluronic acid instillation.

UD: urethral dilatation.

Table 1. The infecting organisms identified on urine microscopy and culture, and the antibiotics used as per the sensitivities for all 22 patients with uncomplicated recurrent urinary tract infection.

Organism	<45 years (seven patients)	Sensitivities and treatment	>45 years (15 patients)	Sensitivities and treatment
<i>Escherichia coli</i>	6 (86%)	Nitrofurantoin Trimethoprim Amoxicillin	13 (86%)	Nitrofurantoin Trimethoprim Ciprofloxacin Cefradine Amoxicillin
<i>Proteus</i>	1 (14%)	Amoxicillin Cefradine	1 (7%)	Ciprofloxacin
<i>Enterobacter</i>	0		1 (7%)	Ciprofloxacin

to the manufacturer's recommendations). Each instillation was performed using a 50 ml vial of Cystistat® containing 40 mg of sodium hyaluronate instilled into the bladder via a urethral catheter and retained intravesically for one to two hours. Urine dipstick was performed before all instillations and if positive for leucocytes or nitrites or both, was sent for urine culture. If the patient had evidence of infection, this was treated and HA instillation was delayed until negative cultures were obtained. Patients were followed up with urine cultures and symptom assessment every three months for a year in order to identify treatment efficacy and side effects.

We also conducted a literature review about the use of GAGs such as HA and CS in the management of females with recurrent UTIs. We retrieved articles from PubMed up to 2012, that looked into the efficacy, safety and durability of HA and CS in the management of female patients with UTIs.

Results

Our experience

A total of 28 patients were suitable for HA treatment during the time period specified of which 22 completed the full course of treatment and attended follow-up for at least one year. Of the six patients excluded from this review: three patients did not attend appointments to receive treatment,

one patient stopped treatment following a diagnosis of vulvar dermatitis, and treatment was discontinued in two patients as they had persistent evidence of infection preventing HA instillation on several occasions. Neither had confounding factors of interest to note.

All 22 patients were female and aged between 17 and 72 (mean 55; SD ±17.8). All patients had breakthrough UTIs and failed the other treatment strategies mentioned prior to HA instillations. The average frequency of UTIs in this patient group was three UTIs per year prior to HA instillations despite receiving the standard treatment for recurrent UTIs. The commonest infecting organism (86%), irrespective of age, was *Escherichia coli* (Table 1). All recurrent UTIs were caused by the same organism. Patients were started on antibiotics as per sensitivities. Nitrofurantoin was used as a first-line treatment in our trust. The patients on cefradine and amoxicillin had been started on these antibiotics by their general practitioner (Table 1).

Twenty-two patients (100%) received fluid and lifestyle management advice. Eighteen (82%) of our patients received prophylactic antibiotics (7 <45 years of age and 11 >45 years of age) for 3–6 months, depending on antibiotic sensitivity identified from urine microscopy and culture (Table 1). Our standard treatment protocol for prophylactic antibiotics is a three- to six-month course of nitrofurantoin or trimethoprim. There was no cyclical regime used unless

there were breakthrough UTIs and resistance to nitrofurantoin or trimethoprim.

All patients (100%) had ultrasound of the kidneys, ureters and bladder and post-void residual (PVR) assessment. All patients (100%) had normal upper tracts and 14 (64%) received urethral dilatation for high PVR (average 83 ml, SD \pm 61.6 ml). No patients required clean intermittent self-catheterisation. Thirteen patients (59%) were given a trial of oestrogen cream for atrophic vaginitis.

Fourteen of the 22 patients (64%) remained UTI-free at one year follow-up and eight (36%) suffered recurrent proven UTIs.⁹

Of the 22 who completed the course of treatment three reported minimal bladder irritation and one reported right loin pain (18%). These side effects did not cause treatment cessation and resolved spontaneously.

Literature review of the evidence of efficacy and safety of intravesical therapies to prevent recurrent urinary tract infections in females

In 2004, Constantinides et al. described the first case series of patients treated with HA in order to prevent recurrent UTIs.¹⁰ Forty pre-menopausal women were included in the study (mean age 35 years), and received HA instillations weekly for 4 weeks and then monthly for 4 months. Seventy per cent of patients remained recurrence-free at the end of the follow-up period (12.4 months). Compared with UTI rate prior to administration there was a decrease in the mean rate of UTI (4.3 to 0.3, $p < 0.001$) and an increase in the median time to recurrence (96 to 498 days, $p < 0.001$). All patients showed good tolerability to HA and no serious adverse effects were reported. Lipovac et al. described similar results in 2006 in a case series of 20 women who received nine instillations over 6 months with a follow-up period of 47.6 weeks.¹

The first prospective, randomised, double-blinded, placebo-controlled study was conducted by Damiano and colleagues using a combination of intravesical HA and CS. HA-CS was instilled weekly for four weeks then monthly for five months; participants were evaluated regarding infections, symptoms and quality of life over a 12-month follow-up period. A 77% reduction was observed in the UTI rate per year in the treatment group compared with the placebo group ($p < 0.001$). In addition, the mean time to UTI recurrence was significantly shorter in the placebo group (52.7 days vs 185.2 days, $p < 0.001$). Statistically significant benefits in quality of life score and Pelvic Pain and Urgency/Frequency Patient Symptom Scale were also seen in the treatment group.²

Current treatment guidelines recommend low-dose prophylactic antibiotics as a treatment option for recurrent UTIs and a recent, randomised study by De Vita

et al. compared intravesical HA-CS with the current treatment standard.^{4,11} This randomised trial compared intravesical HA-CS with a six-week course of low-dose trimethoprim-sulphamethoxazole and looked at outcomes two and 12 months after randomisation. The HA-CS group showed significant reduction in UTI recurrence (one episode vs 2.3 episodes, $p = 0.02$), improved urinary symptoms, improved quality of life and improved cystometric capacity.¹¹

A further randomised trial that supports the use of HA in the prevention of UTI was performed in catheterised oncology inpatients undergoing radiotherapy for spinal cord compression. During hospitalisation 76.5% of patients who received usual catheter care had a UTI compared with 13.5% of those who were randomised to weekly HA instillations ($p < 0.0001$).¹²

These studies, almost exclusively of female patients, all support the use of intravesical HA or HA-CS for the prevention of recurrent UTIs. We therefore introduced HA instillation as a second-line treatment option for female patients with recurrent UTIs in 2007.

Discussion

Although intravesical HA and HA-CS installation is still being evaluated as a treatment option for female recurrent UTIs and is not mentioned in most current guidelines,¹³ there is a growing evidence base to support its use including three randomised controlled trials (see Table 2). Intravesical GAG replacement therapies seem to be effective for the prevention of recurrent infections in females and may be more effective than prophylactic antibiotics.¹¹

Our literature review identified five studies on the use of GAG in the treatment of recurrent UTIs in females, two of which were randomised controlled trials. All reviewed studies used GAG as a first-line management strategy. These studies described small cohorts of patients with short periods of follow-up.

Given the lack of guidelines on the use of GAG routinely as a first-line strategy, and the high cost of such treatment compared with the conventional therapies, we developed our local protocol on the management of recurrent UTIs in females to include intravesical HA as second-line treatment strategy when one or more conventional management strategies have failed.

In our experience, the use of HA as a second-line management option seems effective and the UTI free rate of 64% in our more complex patient cohort, who did not respond to the conventional methods of treatment, is comparable to those published in the literature (see Table 2).

The cost of each vial of hyaluronic acid is approximately £97.50. In combination with outpatient appointment installation which includes the use of catheters for instillations

Table 2. Studies evaluating the use of hyaluronic acid in the treatment of recurrent UTIs.

Study	Patient number	Mean age	Dose & Regimen	Follow up	Results	Side-effects
Constantinides et al. 2004	Case series n=40	35	40 mg HA, weekly for four weeks, monthly for four months	12.4 months	<ul style="list-style-type: none"> - 70% recurrence-free following HA - Increased time to recurrence and reduced UTI per year following HA ($p<000.1$) 	Nine patients had mild bladder irritation
Lipovac et al. 2006	Case series n=20	27.7	40 mg HA; weekly for four weeks, monthly for five months	47.6 weeks	<ul style="list-style-type: none"> - 65% recurrence-free following HA - Increased time to recurrence and reduced UTI per year following HA ($p<000.1$) 	No serious adverse effects
Vedanayagam et al. 2012	Case series n=22	55	40 mg HA; weekly for four weeks, monthly for two months	12 months	<ul style="list-style-type: none"> - 64% recurrence-free following HA 	No serious adverse side effects
De Vita G, Giordano S. 2012	RCT vs low-dose prophylactic antibiotics n=26	60	HA 800mg + CS 1 g weekly for four weeks then every other week for two doses. Comparison with low-dose antibiotics	2 and 12 months	<ul style="list-style-type: none"> - Significant reduction in UTIs in HA/CS group (1 UTI vs. 2.3 UTIs at 12 months' follow-up ($p=0.02$)) - Significant improvement in symptom score and QoL 	No serious adverse effects
Manas et al. 2006	RCT vs standard care n=71	62.2 (control group) 63.1 (HA treated)	40 mg HA once weekly in patients catheterised for malignant cord compression	During hospital admission (median 19 days)	<ul style="list-style-type: none"> - HA treated group experienced less in-hospital UTIs (13.5%) vs control group (76.5%) ($p<0.0001$) 	No serious adverse effects
Damiano et al. 2010	RCT vs sham instillation n=57	34.8	1.6% HA + 2% CS solution; weekly for four weeks, monthly for five months	3, 6, 9, 12 months	<ul style="list-style-type: none"> - 77% reduction in UTI rate/year in treatment vs. sham group ($p<000.1$) - Mean time to recurrence less in treatment group ($p<000.1$) - Improvement in urinary symptoms and QoL 	No serious adverse effects

HA: hyaluronic acid; CS: chondroitin sulphate; UTI: urinary tract infection; QoL: quality of life; RCT: randomised controlled trial.

and specialist nurse time (£50) the total cost per instillation has been approximated to £147.50. With growing economic constraints the decision to use intravesical GAG replacement treatments should be balanced against the cost and efficacy of current approved therapies such as fluid management and prophylactic antibiotics. We feel that using HA as a second-line therapy is a pragmatic and cost-effective treatment strategy instead of using it as a first-line step. However, further prospective randomised trials with larger numbers of patients and longer follow-up periods are needed to explore the efficacy and cost-effectiveness of this new treatment as first-line for the management of recurrent UTIs in females.

It was not difficult to implement intravesical HA as a treatment strategy into our hospital practice but this was helped by having a dedicated female urology clinic, clearly defined departmental treatment protocols and an experienced specialist nurse.

In our patients four of 22 reported minor, self-resolving side effects and this is similar to published results. Patients should be warned about possible mild bladder or loin pain and the small risk of infection associated with any intravesical treatment. No serious side effects were seen in our series and we could find no reports of serious adverse events in the literature (Table 2).

GAG layer specific therapies for the prevention of recurrent UTIs are still in the early stages of investigation and although they have been proven to be effective, several questions remain to be answered. There are currently no published studies comparing the efficacy of intravesical HA to the combination of HA-CS and no studies have evaluated the efficacy of oral pentosan polysulphate for the prevention of UTIs. Further research is needed on this and further long-term studies are needed as current evidence is limited to follow-up of 11 to 12.4 months (Table 2).

Conclusion

There is growing evidence that intravesical HA and HA-CS are effective for the prevention of recurrent UTIs. We have found that intravesical HA was effective as a second-line treatment, well tolerated with minimal side effects and was easy to deliver in our practice.

Conflict of interest

The authors declare that there are no conflicts of interest.

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