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Prevention of Recurrent Urinary Tract Infections by Intravesical Administration of Heparin

A Pilot Study

Tova Ablove, MD, Manish Patankar, PhD, Songwon Seo, MS

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Abstract and Introduction

Abstract

Objective: To assess the effect of bladder instillations using heparin on the rate of urinary tract infections in women resistant to standard therapy.

Patients and methods: The medical records of all women who received bladder instillations between May 2009 and January of 2010 at the University of Wisconsin urogynecology clinic were reviewed. Eighteen women (mean age 67 years) with a history of recurrent urinary tract infections received intravesical instillations (heparin 40,000 U, 2% lidocaine 8 ml, sodium bicarbonate 4 ml) once weekly for 6 weeks. Patients were considered resistant to standard therapy if their condition failed to respond to chronic suppression antibiotic therapy; they had chronic infections and for this reason could not be placed on chronic suppression; or they were not candidates for chronic suppression due to drug allergies. The number of urinary tract infections was monitored during treatment and for 6 months after therapy. The urinary tract infection rates were compared with the rates of urinary tract infection in the 6 months before treatment.

Results: Seventy-eight percent of patients responded to therapy. Subjects were thought to have responded to therapy if there was a greater than 50% reduction in the rate of urinary tract infection. Other variables reviewed included evidence of chronic infection, hormonal status, glomerular filtration rate, age, body mass index, antibiotic allergies, diabetes, hypertension, and chronic antibiotic therapy during bladder instillations. None of these variables were found to be statistically significant.

Conclusion: Bladder instillations decreased the rate of urinary tract infection in this pilot study; this effect persisted into the post-treatment period. More research is needed to confirm these preliminary findings.

Introduction

Urinary tract infections (UTIs) are defined as a pathologic invasion of the urothelium, usually by bacteria. UTIs are the most common source of bacterial infection [Nicolle, 2008]. Recurrent UTIs are defined as at least three episodes of uncomplicated infection documented in the urine with an isolation of over 103 colony forming units/ml [Albert *et al.* 2004]. The recurrent UTI rate in women is very high. After an initial UTI, more than 25% of women will have a second infection within 3–6 months [Foxman *et al.* 2000; Ronald, 2002]. UTIs account for about 8.1 million visits to healthcare providers each year [Schappert and Rechtsteiner, 2008]. More than 50% of women will have at least one UTI in their lifetime. Antibiotics prescribed to treat UTIs account for 15% of all outpatient prescriptions [Dielubanza and Schaeffer, 2011]. The annual healthcare cost associated with UTIs in the USA is estimated to be over $1.6 billion [Foxman, 2002].

Although the commonality and expense of UTIs justify the need for better treatment and prevention, the patients of most concern are those with chronic recurrent infection, especially those who respond poorly to antibiotic therapy. Recurrent UTIs are traditionally treated with chronic low-dose antibiotic therapy (chronic suppression). In recent years there has been an increase in drug-resistant UTIs [Abrahamian *et al.* 2011; Dielubanza and Schaeffer, 2011; Ho *et al.* 2010; Muvunyi *et al.* 2011]. Drug resistance to antibiotics has become a serious concern; consequently, researchers have begun to focus efforts on finding nonantibiotic treatments for UTIs [Beerepoot *et al.* 2012; Trautner and Gupta, 2012].

The bladder uses several natural defense mechanisms to resist infection. Bacteria are flushed out of the bladder via urination. Low urine pH of urine inhibits bacterial proliferation. The urothelium also defends the bladder from infection by identifying and blocking bacterial adherence [Constantinides *et al.* 2004; Kos *et al.* 2008; Mañas *et al.* 2006; Xu and Dai, 2010]. The glycosaminoglycan (GAG) layer, umbrella cells, and tight junctions that comprise the upper layers of the urothelium work together to make it the most impermeable epithelial surface known [Chen and Tong, 2007].

There is evidence that recurrent UTIs may be linked to abnormalities in the GAG layer [Iavazzo *et al.* 2007]. A number of studies have demonstrated a decrease in UTI rates with bladder instillations using the GAG's hyaluronic acid and chondroitin sulfate [Constantinides *et al.* 2004; Damiano and Cicione, 2011; Lipovac *et al.* 2007]. Bladder instillations with GAGs are also used to treat painful bladder syndrome, an inflammatory disease of the bladder. Heparin sulfate has been found to be safe and effective in small studies as a treatment for painful bladder syndrome [Parsons, 2005; Vij *et al.* 2012; Welk and Teichman, 2008]. Heparin sulfate is chemically similar to chondroitin sulfate and hyaluronic acid. In the current study we have investigated the effect of heparin for the treatment of recurrent UTIs. Heparin was specifically chosen in this study because of its affordable costs and availability. It has a relatively stable shelf life and comprises 15% of the sulfonated GAG layer in humans [Marcolo *et al.* 2006]. Heparin has the highest negative charge of any biologic molecule, which may enhance its antiadherence activity [Cox and Nelson, 2004; Gandhi and Manceral, 2008]. Further there is extensive literature on heparin and its effect on inflammation and immunity [Young, 2008]. Our hypothesis is, bladder instillations with heparin can be effective in the treatment of chronic and recurrent UTIs.

Methods

The study was approved by the Institutional Review Board at the University of Wisconsin hospital and clinics. The medical records of all women who received bladder instillations between May 2009 and January 2010 at the University of Wisconsin urogynecology clinic were reviewed. There were 18 women (mean age 67 years) with a history of recurrent UTIs who were considered resistant to conservative therapies because they were either ineligible or not responding to chronic suppressive antibiotics. These patients received intravesical instillations (heparin 40,000 U, 2% lidocaine 8 ml, sodium bicarbonate 4 ml) once weekly for 6 weeks. The bladder was drained of urine, and 250 ml of sterile water was instilled and drained. The heparin solution was then instilled and held in the bladder for 1 h before voiding. The number of infections 6 months prior, during, and 6 months post infection were recorded. Urinalysis and cultures were taken on patients who complained of symptoms of infection. These were clean catch specimens. If a subject was unable to provide a specimen confirmed by urinalysis a catheterized specimen was taken. All patients with positive urine cultures were treated with culture-sensitive antibiotics. All patients were instructed to have their urine cultures done at our institution. Under extenuating circumstances when cultures were taken outside of our institution, subjects contacted the clinic so that culture results could be faxed and scanned into our system. Data extracted from the electronic medical record included dates of infections and bacteria grown in culture. If a patient was considered to have a chronic infection this was noted, along with antibiotic sensitivities. Patients were considered to have a chronic infection if they were infected with the same pathogen in each culture in the 6 months prior to treatment and were infected at the time of the first instillation. Descriptive data on the patients were also retrieved, including medical conditions, medications, allergies, hormonal status, hormone replacement therapy (HRT), use of chronic suppression therapy, body mass index (BMI), blood urea nitrogen (BUN), creatinine, and glomerular filtration rate. Patients were considered to have responded to therapy if there was a 50% or greater reduction in infection rate after therapy. These 'responders' either did not require additional therapy or now responded to traditional therapy, such as local estrogen and chronic suppressive antibiotics. Other variables reviewed included evidence of chronic infection, chronic suppression therapy, hormonal status, kidney function, medications, BUN, creatinine, menopausal status, body mass index, glomerular filtration rate, and chronic medical conditions. The Wilcoxon rank sum test and Fisher's exact test were performed for the comparison of numerical variables and categorical variables respectively.

Results

Of the 18 subjects, 13 responded to therapy, 78% (95% confidence interval 52–94) (Figure 1). Five out of 13 patients then were controlled with chronic suppressive therapy after treatment; the rest did not require any additional treatments. Patients were divided into two groups, those who responded to bladder instillations and those who did not. Prior to therapy, nonresponders *versus* responders had 4.6 ± 2.0 *versus* 4.2 ± .84 UTIs in the prior 6 months respectively. After therapy, nonresponders *versus* responders had 3 ± 0 *versus* 0.6 ± .96 in the 6 months post therapy. The average age was 67 years. The average BMI was 33.4. The average glomerular filtration rate was 69. None of these parameters were statistically different between the groups (). Other characteristics examined included antibiotic allergies, evidence of chronic cystitis, diabetes, hypertension, and chronic suppressive antibiotic therapy. None of these parameters were statistically different between the groups (, 3) (Figure 2, 3). Patients with either exogenous (systemic or local HRT) or endogenous (premenopausal) estrogen were compared with those who were postmenopausal and not on HRT to see whether the presence of estrogen at the time of and during therapy improved response rates. There was a trend toward improved response with estrogen (p = 0.082,). No subjects reported adverse reactions to therapy and no subjects dropped out prior to completing all six treatments.

Table 1. Patient characteristics: numerical data.

		Response to heparin bladder instillations		Total (*n* = 18)	*p* Value
		No (*n* = 4)	Yes (*n* = 14)		
GFR	Mean ± SD	65.75 ± 19.55	70.23 ± 23.65	69.18 ± 22.25	1
	Median	69	66	69	
BMI	Mean ± SD	32.55 ± 4.65	33.69 ± 9.61	33.44 ± 8.64	0.75
	Median	33.75	32.8	33.38	
Age	Mean ± SD	72.25 ± 7.14	66.43 ± 14.40	67.72 ± 13.19	0.394
	Median	74.5	70.5	71.5	

BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation.

Table 2. Patient characteristics: categorical data.

	Response				Total (*n* = 18)		*p* Value
	No (*n* = 4)		Yes (*n* = 14)		*N*	%	
	N	%	*N*	%			
ABX allergies							
No	2	50	7	50	9	50	1
Yes	2	50	7	50	9	50	
Chronic infection							
No	3	75	9	64	12	67	1
Yes	1	25	5	36	6	33	
ABX therapy							
No	3	75	10	71	13	72	1
Yes	1	25	4	29	5	28	
Estrogen							
No	4	100	5	36	9	50	0.082
Yes	0	0	9	64	9	50	
DM							
No	3	75	9	64	12	67	1
Yes	1	25	5	36	6	33	
HTN							
No	0	0	5	36	5	28	0.278
Yes	4	100	9	64	13	72	

ABX, antibiotic; DM, diabetes mellitus; HTN, hypertension

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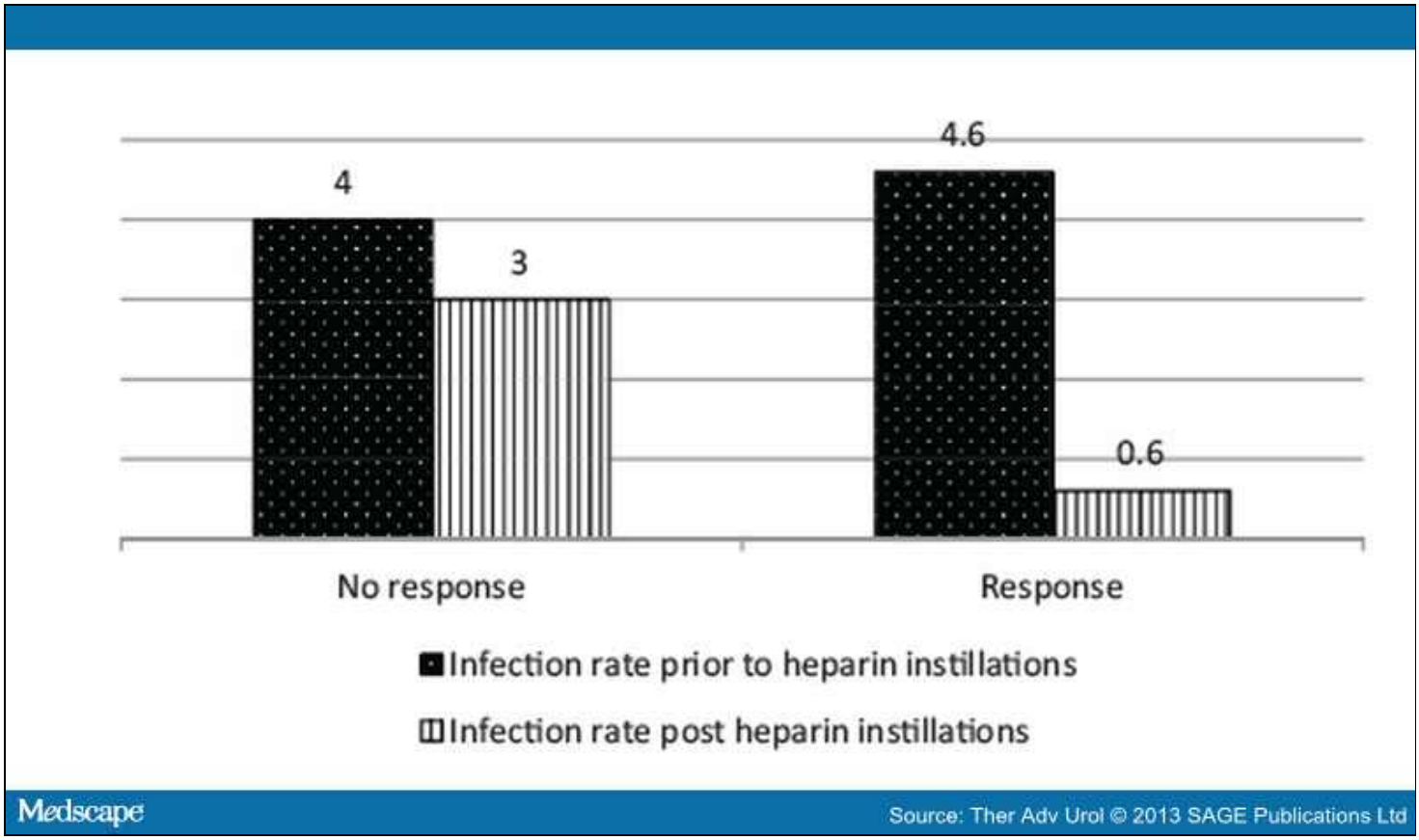

Figure 1.

Infection Rate Before and After Treatment. Infection rate prior to heparin instillations: the average number of infections over the 6 months prior to heparin bladder instillations. Infection rate post heparin instillations: the average number of infections over the 6 months after heparin bladder instillations were completed. The numbers over each column represent the mean for that group.

Discussion

Recurrent UTIs are a common in women, difficult to treat, and result in a great deal of patient morbidity and healthcare cost. The purpose of this study was to determine the effectiveness of heparin instillation in the treatment of chronic and recurrent UTIs that have failed to respond to antibiotic treatment.

The cohort of patients evaluated in this study is unique because they represent the 5% of women whose condition fails to respond to chronic suppression therapy. Failures were divided into three groups. First, patients with breakthrough infections on chronic suppression over the course of 3–6 months. These patients were on standard chronic suppression therapy with either macrodantin 50 mg nightly or bactrim half a tablet nightly. Second, others were considered treatment failures since chronic infection prevented the use of suppressive antibiotic therapy because there was no documented infection-free period. These women were repeatedly treated for cultureproven UTI with sensitive antibiotics and had positive post-treatment urine cultures within 1 month of antibiotic therapy. Third, the last group could not be started on chronic suppression because of drug intolerance and antibiotic allergies. Seventy-eight percent of our study subjects responded to heparin bladder instillations with a greater than 50% reduction in the number of UTIs in the 6 months after treatment.

We found UTI infection rates fell from 4.4 infections in the 6 months before treatment to 1.1 infections in the 6 months after treatment when all subjects were analyzed together.

Patients on chronic suppression therapy with breakthrough infections were not excluded from the study and were not asked to discontinue antibiotics prior to starting heparin instillations. On analysis of the data there was an equal percentage of patients on chronic antibiotic therapy in both groups.

Although we did not control for cranberry use in the inclusion criteria for this study, in reviewing our data, eight out of 10 responders were taking cranberry and four out of five patients whose condition failed to respond to treatment. The use of cranberry did not have an effect on the response of subjects to heparin bladder instillations. Our findings are consistent with current knowledge. Jepson and colleagues recently updated their review on the effect of cranberry on the rate of recurrent UTIs and found that 'Cranberry juice cannot currently be recommended for the prevention of UTIs. Other preparations (such as powders) need to be quantified using standardized methods to ensure the potency, and contain enough of the "active" ingredient, before being evaluated in clinical studies or recommended for use' [Jepson *et al.* 2012].

We acquired descriptive statistics on the study subjects, looking for any factor which may affect the response to treatment. Statistical significance was not found in medical conditions like diabetes, and chronic kidney disease between responders and nonresponders. We examined post-void residual volumes, urine pH, and urine flow and did not see any significant difference in our study group compared with the average patient with incontinence without bladder infections. We also did not see any difference between the groups in the study. We monitored the urine cultures for infecting pathogens to see if there was a correlation between pathogen and response. Furthermore, we did not observe any correlation between chronic infections (infected at the time of the first instillation, the same pathogen each culture) or multiple allergies with response to heparin instillation. However, this lack of statistical significance cannot be equated to the lack of the proof in this study due to the small sample size. The only comparison that trended toward significance was improved response to instillations in women with endogenous estrogen and women on local estrogen replacement therapy, prior and during treatment.

There have been other studies which demonstrated a reduction in UTI rates with the instillation of GAGs into the bladder [Constantinides *et al.* 2004; Damiano and Cicione, 2011; Iavazzo *et al.* 2007; Lipovac *et al.* 2007]. These studies have also shown a prolonged response to treatments, with the effects of treatments lasting greater than 6 months. Constantinides and colleagues reported on the prevention of UTIs in women with recurrent UTIs using hyaluronic acid for 5 months. They noted a fall in UTIs from 4.5 per year prior to therapy to 0.3 per year in the year during and after therapy Constantinides *et al*. 2004]. Lipovac and colleagues also evaluated the effect of hyaluronic acid bladder instillations over 6 months. They reported a fall in UTI infection rates from 4.99 to 0.56 per year in the year during and after therapy [Lipovac *et al*. 2007]. Damiano and Cicione performed a randomized, placebocontrolled trial reporting on the effects of hyaluronic acid and chondroitin sulfate bladder instillations. They found a 77% reduction in the rate of UTIs compared with placebo [Damiano and Cicione, 2011].

We expected patients with multiple antibiotic allergies to be easier to treat and patients with chronic infection, kidney disease, and diabetes to be more difficult to treat. None of these factors appeared to be a variable in predicting who would respond to heparin bladder instillations. It is possible that glycemic control may have affected response rates to therapy. Four subjects had hemoglobin A1c (HbA1c) levels recorded in their electronic medical record during the time of the study. There was one nonresponder (HbA1c: 6.0) and three responders (HbA1c: 5.6, 5.6, and 9.0). This dataset is very small. Diabetes is a known risk factor for UTIs and its effect on the efficacy of heparin instillations warrants further study.

Although significance was not achieved, there was a trend in our data toward an improved response to therapy in patients on either endogenous (premenopausal) or exogenous estrogen. There is some support in the literature for this finding. Estrogen is known to decrease bladder permeability [Parekh *et al.* 2004]. Anand and colleagues have shown that a lack of estrogen decreases the thickness of the GAG layer and interferes with the synthesis of GAG molecules [Anand *et al*. 2012]. A thinner GAG layer also decreases the GAG's ability to prevent bacterial adherence and explains the increase in UTI rates in women who are postmenopausal.

In our cohort 84% (15 out of 18) of patients were postmenopausal. It is known that women who are postmenopausal have a higher incidence of UTIs and are less tolerant to antibiotic therapy [Dielubanza and Schaeffer, 2011; Nys *et al.* 2006; Ronald, 2002]. The high rate of women who were menopausal in this cohort may also in part be due to the demographics of the referral practice from which subjects were recruited. It is also possible that because these are the patients most resistant to therapy, they make up the majority of the cohort. Prior studies with intravesical instillation of GAG proteins have shown a good response in younger patients. In the study by Constantinides and colleagues the average age of women was 35 years and they showed significant decreases in infection rates that lasted for over 6 months post therapy [Constantinides *et al*. 2004].

The GAG layer prevents bacterial adherence [Gu and Wang, 2008]. GAGs are thought to play a role in stimulation of the immune system by promoting the activation and movement of leucocytes in inflamed tissues [Gu and Wang, 2008]. GAGs also act as carriers/presenters of chemokines and growth factors [Gandhi and Mancera, 2008; Ley *et al.* 2007]. These functions act to stimulate the immune system and help the bladder resist infection. They may also explain why the effect lasts for months after treatment.

The strength of the study, aside from the good response rate to treatment, was that subjects were followed for over a year; 6 months before treatment and 6 months after treatment. Also, given the study design, each subject could act as their own control.

The weaknesses of the study are the small sample size, the retrospective design, and the lack of a true control group. It is possible that other factors observed may also affect response but the study power was limited by the small cohort size. Our ongoing trials are focused on recruiting additional cohorts to confirm the trends in positive associations observed in this initial study.

Conclusion

Heparin bladder instillations appeared to be effective and well tolerated in patients with recurrent UTIs who were resistant to conservative therapy in this initial pilot study. This effect persisted into the post-treatment period.

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