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Intravesical instillations for the treatment of refractory recurrent urinary tract infections

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Abstract

Background: Treatment options for refractory recurrent urinary tract infections (UTI) are limited; therefore, we sought to determine if intravesical instillations with heparin effectively treat recurrent UTIs.

Methods: Patients at an academic medical center who received intravesical instillations with heparin for recurrent UTIs/chronic cystitis between January 2011 and December 2015 were identified *via* International Classification of Diseases, Ninth Revision (ICD-9) and Current Procedural Terminology (CPT) procedure codes. All cases were analyzed for frequency of UTIs during the treatment phase as well as for the subsequent 6 months after completion of therapy. Demographic, clinical and treatment related factors were then collected from the medical records to draw associations with success or failure of treatment.

Results: Thirty-nine women were treated with heparin intravesical instillations for recurrent UTIs. The average age of the cohort was 68.38 years [range 25–88, standard deviation (SD) 12.92], with mean parity 2.38 (range 0–7, SD 1.55) and mean body mass index 27.85 (range 19.5–37.9, SD 4.84). A total of 84.6% completed the recommended 6-week treatment course while 69.2% went on to an additional maintenance phase. Twelve patients (30.8%) had a culture-proven UTI during the treatment phase. In the 6-month follow-up period, 46.2% of patients had at least one UTI with only seven patients (17.9%) meeting criteria for recurrent UTIs (two or more UTIs in 6 months). On univariable assessment, development of recurrent UTIs after completion of instillation therapy was associated with increasing age and vaginal estrogen use during the instillation treatment course.

Conclusions: Intravesical instillation with heparin is an effective option to consider for the treatment of refractory recurrent UTIs.

Keywords: heparin, instillations, recurrent urinary tract infections

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Introduction

Recurrent urinary tract infections (UTIs) are becoming a public health obstacle given the increasing incidence of these infections in our aging population as well as the cost burden associated with treatment. It is estimated that the lifetime risk for a woman to develop a UTI is over 50%.¹ Once diagnosed, a woman has a 25% risk of having a repeat infection in the following 3–6 months.² A patient is deemed to have recurrent UTIs once she has three or more culture proven infections in the preceding 12 months or two infections in the prior 6 months.³ Once diagnosed with recurrent UTIs, physicians typically recommend

prophylactic regimens to decrease the rate of subsequent infections.

There are a number of effective prophylactic regimens available to treat and prevent recurrent UTIs, including cranberry supplementation, continuous low-dose antibiotics, daily methenamine use and vaginal estrogen application.⁴ Unfortunately, despite compliance with these methods, a percentage of women still continue to have recurrent UTIs.

The pathophysiology of UTIs and recurrent UTIs is multifactorial. Many people believe that a

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component of its development may be due to abnormalities of the bladder's transitional epithelium, specifically the glycosaminoglycan (GAG) layer.⁵ An initial insult damages this layer, which subsequently allows bacteria to adhere, proliferate and cause symptomatic infections.⁶ A similar pathway has been theorized to lead to the development of interstitial cystitis/bladder pain syndrome (IC/BPS). Restoration of the GAG layer has been more widely studied in patients with IC/BPS, with various intravesical instillations leading to positive results. Given a similar mechanism of development, a small number of European groups have evaluated the utility of using hyaluronic acid (HA) and chondroitin sulfate (CS) (both considered glycosaminoglycans) in the treatment of recurrent UTIs with excellent results.⁷⁻¹¹

Intravesical instillations with HA and CS are currently not available for use in the United States. Fortunately, heparin sulfate is chemically similar to HA and CS and has previously been shown to successfully treat interstitial cystitis/bladder pain syndrome.¹² Given parallel mechanisms of action, we hypothesize that intravesical heparin instillations can effectively treat women with refractory recurrent UTIs.

Methods

This case series was approved by the Institutional Review Board at the University of California, Irvine Medical Center. The medical records (electronic and written) of women with recurrent UTIs who received intravesical instillations of heparin between January 2011 and December 2015 were reviewed.

Heparin instillations consisted of 10,000 units of heparin mixed with 250 mg solumedrol, 2 ml of 4% lidocaine and 50 ml of sterile water. Instillations were typically performed by the nursing staff. Each patient would have her bladder drained of urine with a sterile catheter and then the solution would be instilled into the bladder using the same, previously placed catheter. Patients would then be instructed to hold the cocktail for at least 60 min prior to voiding. A full 'treatment course' of instillations included 6 weekly instillations.

Patients in this case series typically provided clean catch or catheterized specimens with onset of any symptoms. Patients were asked to coordinate all of their UTI care at the University of California, Irvine Medical Center.

Thereafter, treatment-related factors were collected, including compliance with 6 weekly instillations, any maintenance treatments that were provided, number of culture proven urinary tract infections (>100,000 colony forming units) during the treatment course and number of infections within 6 months of completion of a treatment course of instillations. Several other demographic and clinical factors were collected from the medical record as well.

Using SPSS statistical software (version 24), Wilcoxon–Mann–Whitney tests were performed for continuous independent values while Fisher's exact tests were calculated for categorical independent variables. Statistically significant values were noted to have a *p* value less than 0.05. Multivariable logistic regressions were not performed given the overall small sample size of this cohort.

Results

During the study period, 39 patients received the heparin/solumedrol instillation for treatment of refractory, recurrent UTIs. The average age was 68.38 years [range 25–88, standard deviation (SD) 12.92], with mean parity of 2.38 (range 0–7, SD 1.55) and mean body mass index (BMI) of 27.85 (range 19.5–37.9, SD 4.84). The remaining demographic and clinical criteria collected for each group are listed in Table 1.

In this cohort, 84.6% of patients completed 6 weekly instillation sessions with 69.2% receiving at least three maintenance instillations thereafter (each instillation at least 2 weeks apart). The number of UTIs, both during the treatment phase and the subsequent 6 months after completion of treatment, were calculated. Twelve patients (30.8%) had a culture-proven UTI during the treatment phase. In the 6-month follow-up period, 46.2% of patients had at least one UTI, with seven patients (17.9%) meeting criteria for recurrent UTIs (two or more UTIs in 6 months) (Table 2).

Univariable assessments were performed to determine associations between lack of response to treatment (characterized as having a UTI during instillation, having a UTI in the 6 months after completion of treatment and having two or more UTIs in the 6 months after completion of treatment) and demographic or clinical factors (Table 3). When looking at patients who had UTIs during their instillation treatment course, a lack of

Table 1. Demographic and clinical criteria of cohort.

	N (%)
Age	M 68.38 years (R 25–88 years)
Parity	M 2.38 (R 0–7)
BMI	M 27.85 (R 19.5–37.9)
Current or prior smoking	7 (18.42)
Any vaginal delivery	30 (81.08)
Any cesarean section	3 (8.11)
Increased frequency (>7/day)	24 (61.54)
Nocturia (>1/night)	20 (51.28)
Pad use	13 (33.33)
Urge incontinence	25 (64.1)
Stress incontinence	24 (61.54)
Self catheterization	5 (12.82)
Fecal incontinence	11 (28.21)
History of hysterectomy	20 (51.28)
History of bilateral salpingo-oophorectomy	14 (35.9)
History of pelvic organ prolapse surgery	12 (30.77)
History of mid-urethral sling placement	7 (17.95)
Currently sexually active	14 (41.18)
Vaginal estrogen use prior to instillations	25 (64.1)
History of diabetes mellitus	9 (23.08)
History of neurological disorder	6 (15.38)
Current steroid use	1 (2.63)
Anterior vaginal wall prolapse, stage	
0	12 (34.29)
1	7 (20)
2	14 (40)
3	2 (5.71)
Posterior vaginal wall prolapse, stage	
0	13 (37.14)
1	14 (40)
2	8 (22.86)
Apical prolapse, stage	
0	25 (69.44)
1	8 (22.22)
2	2 (5.56)
3	1 (2.78)
Post void residual	M 73.51 ml (R 2–300)
Vaginal estrogen use during instillations	21 (58.33)
Any antibiotic use during instillations	13 (33.3%)

M, mean; R, range.

Table 2. Percent of patients with urinary tract infection (UTI) during instillations and after completion of treatment course of instillations.

	N (%)
UTI during instillations	12 (30.8)
Any UTI in the 6 months following treatment	18 (46.2)
Two or more UTIs in the 6 months following treatment	7 (17.9)

Table 3. Selected demographic and clinical criteria associated with lack of response to heparin intravesical instillation treatment during instillation treatment phase and factors associated with persistent recurrent urinary tract infections (UTIs) following completion of instillation therapy.

	p value	
	UTI during instillations	Two or more UTIs in the 6 months after instillations
Increasing age	0.284	0.005
Anterior vaginal wall prolapse	0.044	0.743
Increasing post void residual	<0.001	0.086
Vaginal estrogen use during instillations	0.494	0.027
Any antibiotic use during instillations	0.008	0.664

response was significantly associated with having an anterior vaginal wall defect ($p = 0.044$), a rising postvoid residual ($p < 0.001$) and any antibiotic use during the treatment course ($p = 0.008$). No clinical or demographic variables were associated with having at least one UTI during the follow-up period; however, when stratified to patients meeting criteria for recurrent UTIs, increasing age ($p = 0.005$) and vaginal estrogen use during the instillation treatment course ($p = 0.027$) were associated with recurrent UTIs.

Discussion

In our case series of 39 women with refractory UTIs despite compliance with conservative treatments options, 53.8% of women had no UTIs

following treatment with intravesical heparin instillations while only 17.9% met criteria for recurrent UTIs. Three of these patients were infected with pan-sensitive organisms following treatment, while the remaining four patients were infected with bacteria that were resistant to one or more antibiotics. Overall, instillations appear to be effective for most patients. Despite its invasive nature compared with medications or vaginal estrogen cream, no adverse events were identified or documented to merit discontinuation of treatment.

Most of the literature for use of intravesical instillations is in the realm of IC/BPS. The pathophysiology of IC/BPS is poorly understood; however, one of the theorized pathways is due to abnormalities of the GAG layer of the urothelium, a hydrophilic coating and barrier within the bladder.¹³⁻¹⁵ Due to the decreased integrity of this layer, otherwise benign urinary solutes can permeate the urothelium and stimulate the underlying nerves and smooth muscle causing pain and hypersensitivity.^{13,15} Following restoration of the GAG layer of the bladder using Dimethyl sulfoxide (DMSO), heparin¹² or pentosan polysulphate, a subset of patients report an improved pain profile.¹⁶ Given this, the current American Urological Association (AUA) guidelines report that intravesical instillations are second-line treatment options for IC/BPS.¹⁶

The pathophysiology of recurrent UTIs is also complex, depending on several genetic, environmental and behavioral factors. It has been postulated that an abnormal GAG layer in the bladder may also be implicated in the development of recurrent UTIs.^{17,18} Bacteria can easily adhere to the bladder, proliferate and cause recurrent infections due to this porous epithelium.¹² Cystoscopic changes in urothelial morphology are evident following a 6-month treatment with HA and CS instillations for recurrent UTIs. Costantini and colleagues demonstrated that diffuse and localized hyperemia as well as 'whitish areas' of the trigone resolved upon treatment.¹⁹

Research out of Europe has shown an improved infection profile with the use of HA with or without CS. Both HA and CS are components of the bladder's GAG layer and therefore have been used for both treatment of IC/BPS and recurrent UTIs. A meta-analysis including results from two prospective studies and two retrospective studies out of Europe evaluated 143 women with

recurrent UTIs. This study showed a statistically and clinically significant mean decrease in UTIs per year of 3.4.²⁰ A subsequent retrospective study of 157 women reported similar findings, with a decrease in UTI rate from 4.13 to 0.44 per year.¹¹ Thereafter, a case control study was published comparing HA and CS to standard medical management as advised by the European Association of Urology. A total of 181 women received intravesical instillations and 95 received standard treatment. Within the instillation group, there was a 49% reduction in bacteriologically confirmed recurrence, defined as having at least one UTI in the following 12 months.²¹

Unfortunately, HA and CS are not readily available in the United States thereby limiting its use in our refractory population. More importantly, many of the previously mentioned studies had very restrictive exclusion criteria: patients were excluded if they were 80 years of age or older, had a Post void residual (PVR) greater than 50 ml, were currently on concurrent prophylactic antibiotics, or had a history of diabetes, steroid use, immunosuppression or functional/anatomic abnormalities of the urinary tract.⁷⁻¹⁰ Typically, these patients are the ones that are the hardest to treat and need alternative interventions. Notably, for the studies included in the De Vita meta-analysis, three of the four studies had an average age of 27–35, with only one having an average age of 60.1 years.²⁰ Unfortunately, the etiology of recurrent UTIs varies depending on the menopausal status, with postmenopausal women having an overall higher incidence of recurrent UTIs.

Above and colleagues evaluated the utility of heparin instillations for the treatment of refractory recurrent UTIs in 18 women.²² Following 6 weekly treatments, 78% of women had a greater than 50% reduction in infections, going from 4.4 to 1.1 infections over a 6-month time period.²² The average age of this cohort was 67 years with a BMI of 33.4.²² There was no clinical or demographic criterion associated with success, although estrogen use (systemic and local) trended towards an improved response.²²

In our cohort, 46.2% of patients had one or more infections following treatment, while only 17.9% met criteria for recurrent UTIs. Patients were also more likely to be postmenopausal and overweight by BMI. Therefore, similar to Above's study, we show an 82.1% reduction in rate of recurrent UTIs, a term that we argue is more

widely translatable: patients who continue to meet criteria for recurrent UTIs will be offered more aggressive treatment while those who do not meet criteria will be managed conservatively/expectantly.

During our univariable analysis, we noted that increasing age and vaginal estrogen use were associated with persistent recurrent UTIs. Postmenopausal status is a well known risk factor for recurrent UTIs. In Cicione and colleagues' retrospective study evaluating HA instillations, they reported that women over the age of 50 were 3.41 times more likely to have new UTI episodes following treatment.¹¹ Yet, this is likely a multi-fold issue. With an increase in age, there is also an increase in institutionalization for other comorbidities and decreased functional status,²³ in addition to a lack of estrogen, all of which may contribute to development of UTIs.

Vaginal estrogen supplementation is a well known option for treatment and prevention of recurrent UTIs, supported by a recent Cochrane meta-analysis. Lack of estrogen leads to atrophic vaginal epithelium as well as an increased vaginal pH and decreased endogenous vaginal flora (lactobacillus).²⁴ Several basic science studies have also reported on the effect of postmenopausal status and estrogen on the bladder. In histological studies of the rabbit bladder following oophorectomy, there was a marked decrease in mucosal blood flow, increased hypoxia and marked increased mucosal permeability, all factors that can be attributed to the increased rate of UTIs.²⁵ Subsequent estrogen therapy led to increased blood flow to both the urethra and bladder neck.²⁵ Additionally, in a murine model, estrogen treatment was associated with a quicker response to bladder infection that likely helps with wound repair following infection.²⁶

Although this analysis is limited due to its retrospective design, small sample size and lack of a control group, the data are not only reassuring but encouraging as well. Given that heparin works on the bladder urothelium in a similar pathway as HA and CS, it is likely that it will have a similar effect on recurrent UTIs as the larger European studies have reported on. Additionally, despite the weekly nature of treatments and need for catheterization to administer medications, patients respond well to treatment with no side effects. Given that our study, as well as the previously published international work, report excellent tolerability of this

intervention, we can postulate that refractory patients will likely respond well to this treatment.

Overall, these results are promising. In order to truly determine the utility and safety of intravesical instillations, a prospective comparative study will need to be performed to show a valid resolution or decrease in recurrent UTI rates. Ideally, this study would compare the heparin cocktail to a sham instillation for patients meeting criteria for recurrent UTIs despite compliance with conservative measures. Thereafter, patients should be followed over 6–12 months to determine frequency of infections and side effects. Ideally, a predetermined maintenance phase should be followed during the trial as well, similar to the European studies where patients at a minimum had monthly maintenance instillations for 6 months.

Conclusion

To date, this is the largest cohort of patients with refractory recurrent UTIs who have been treated with intravesical heparin instillations and systematically evaluated for treatment response. We have shown that following a 6-week treatment course (with or without a maintenance phase), a large majority of patients no longer meet criteria for recurrent UTIs. These are promising data in the age of antimicrobial resistance and the strong desire for interventions that can treat infections without exposing patients to a prolonged course of antibiotics (and their subsequent side effects that can lead to decreased compliance). Many institutions have patients with recurrent UTIs that are refractory to traditional management. Intravesical instillations may be a treatment strategy that can be employed for this difficult to treat population.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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