

Treatment of Recurrent Bacterial Cystitis by Intravesical Instillations of Hyaluronic Acid

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Purpose: To evaluate the results of intravesical instillations of hyaluronic acid (HA) in the treatment of recurrent bacterial cystitis (RBC), and to assess the rate of tolerability, the rate of recurrence of RBC and side effects of treatment.

Materials and Methods: The study included 23 female patients from September 2012 to May 2013, aged 28-42 years. Twenty three women with a history of RBC, received intravesical instillations of HA once weekly for 6 weeks then once monthly for 8 months.

Results: In 16 (69.6%) of patients, symptoms of RBC resolved after 8 months. In 5 (21.7%) patients after 8 months of HA treatment, urgency was reduced only by 30%. Therefore, it was decided to use combined therapy of HA and alpha blockers in this cohort group. There was a specific reduction (75%) in frequent urination at day and at night without urgency. Despite the use of above mentioned treatment, in 2 (8.7%) patients, RBC was still present and therefore the treatment was discontinued.

Conclusion: The use of HA protects mucosa of urinary bladder and alleviates symptoms of infection. The intravesical instillations of HA and combination of HA + alpha blockers seems to be an effective therapeutic alternative in patients with RBC.

Keywords: anti-bacterial agents; administration; therapeutic use; drug therapy; female; recurrence; urinary tract infections.

INTRODUCTION

The recurrent bacterial cystitis (RBC) is characterized by persistent symptoms like pain, urgency, and frequency. It is still a challenge to find an effective, suitable therapy in clinical practice. Hyaluronic acid (HA) has a long-term positive effects on treatment of symptoms of RBC. The glycosaminoglycan (GAG) layer on inside surface of urinary bladder is thought to be protective against microorganisms, carcinogenic substances, microcrystals and other agents in urine. It is also claimed that it is a natural defense mechanism, protecting epithelium of urinary bladder against irritating agents in urine. The cavities in protecting layer GAG, covering the epithelium of urinary bladder may disturb its protecting functions and they may cause adherence of bacteria, microcrystals, molecules of proteins and iron to epithelium of urinary bladder wall. HA temporarily replaces the deficient GAG layer of the bladder wall which helps to relieve the symptoms of pain, frequency and urgency. Urinary tract infections (UTIs) are among the most common bacterial infections, affecting women at a much higher frequency than men.^(1,2) Estimates suggest that about a third of women will have at least one episode of UTI requiring antibiotic therapy by the time they are 24 years old, and over a lifetime a half of them will have at least one UTI.^(1,3) There is also a high level of recur-

rence of UTI and 25-35% of initial UTI episodes will be followed by a recurrent infection within 3-6 months.^(2,4) Although UTIs have traditionally been managed by intermittent or prolonged antibiotic therapy,^(2,6) increasingly there is a renewed interest in the mechanisms of UTI and the development into recurrent infections.

MATERIALS AND METHODS

Study Population

In a preliminary study, 56 women suffering from cystitis were subjected to antibiotic therapy. In 23 patients, the antibiotic therapy was not efficient and there were recurrences. These patients were qualified to the treatment by intravesical instillations of HA. The study included 23 female patients from September 2012 to May 2013, aged 28-42 years. Twenty three women with a history of RBC, received intravesical instillations of HA once weekly for 6 weeks then once monthly for 8 months.

Inclusion and Exclusion Criteria

The inclusion criteria were: age between 20-50 years, routine negative urine examination and urine culture, normal blood chemistry tests and cystitis symptoms last over 1 month. The exclusion criteria were: pregnancy, cystitis symptoms caused by known reasons such as bladder tumor, previous operation, acute cystitis, urethral stenosis, incapable to provide informed consent due to neurological or psychological disorder.

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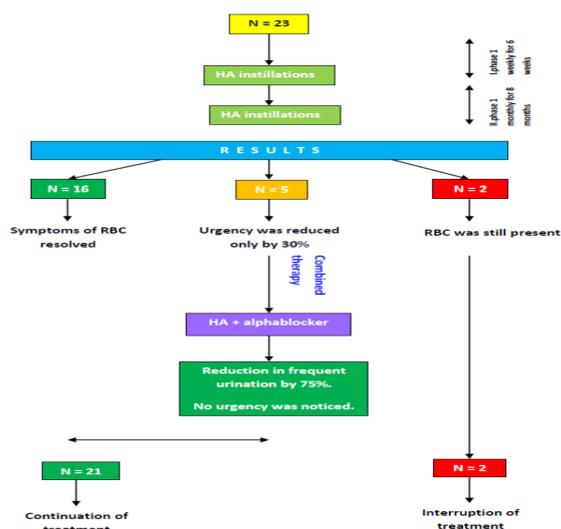


Figure 1. Overview of the study and results.

ders, poor compliance and severe alcoholism or drug addiction, a known sensitivity to any component of the HA preparation used for bladder instillation. Woman (28 > years old) recruited for the study were referred to the outpatient clinic of the author's institution specifically for the treatment of RBC, and had been followed in the department for this problem for at least a year. All patients had a thorough clinical and radiological evaluation. The former was designed to exclude patients with urethral stenosis or external genitourinary abnormalities. The radiological examination included ultrasonography, and flexible cystoscopy.

Treatment

Twenty three women (mean age 35 years, range 28-42, SD 4.16) with a history of RBC, received intravesical instillations of HA (40 mg in 50 mL NaCl solution) once weekly for 6 weeks then once monthly for 8 months. In 5 (21.7%) patients after 8 months of HA treatment, urgency was reduced only by 30%. Therefore, it was decided to use combined therapy of HA and alpha blockers (tamsulosin 0.4 mg once daily) in this cohort group (**Figure 1**). The HA instillations were administrated using a sterile single-use catheter and a sterile instillation gel. The patients were recommended not urinating for at least 1 to 2 hours. No prophylactic antibiotic was given before, during, or after bladder instillations.

Outcome Measures

There were 3 follow-up times from starting HA instillations. After 6 weeks, 3 months and 8 months of treatment, presence of UTI was checked by urine culture taken before catheterization and instillation. In addition, patients rates their pre- and post- treatment as well as their present symptoms, and the level of pain was determined on a 100 mm visual analog scale (VAS, 0-10). All of the patients were asked to comment on their personal benefit on quality of life. Response to therapy was assessed using a questionnaire administrated to all patients at baseline and at each hospital visit. The questionnaire assessed day- and night-time urinary frequency. All patients were given a diary and asked to record relevant symptoms between visits. The primary outcome measures were the number of UTIs per patient per year and the mean time to UTI recurrence at the report-

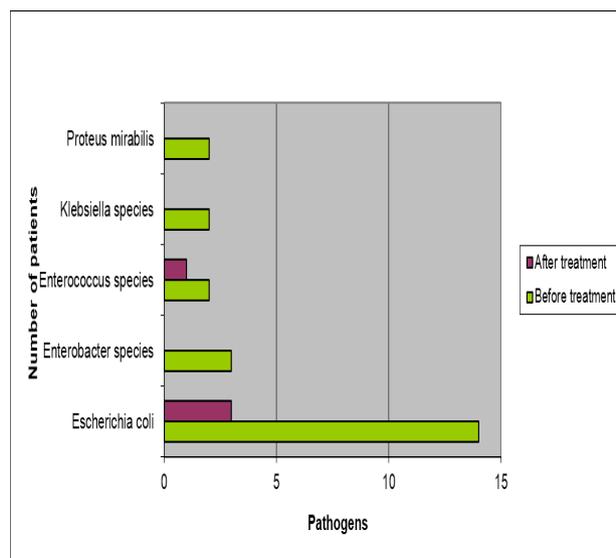


Figure 2. The type of pathogens identified during infections.

ed longest follow-up. The secondary outcome measures were 24h urinary frequency (number of voids in one day) and the Pelvic Pain and Urgency/Frequency (PUF) symptoms assessed using the PUF symptom scale.

Statistical Analysis

For the statistical analysis, the number of UTIs was calculated for the retrospective (before HA) and prospective (after HA treatment) phases of the study. Continuous variables were compared using the Wilcoxon rank-sum test. The time to recurrence of infection before and after HA therapy was analyzed using a Kaplan-Meier survival function; in the retrospective assessment (before HA) this was defined as the mean time elapsed between each infection, and in the prospective assessment (after HA) as the time elapsed between the first HA instillation and the first recurrent infection. Differences in continuous variables were expressed as mean difference (MD) with 95% confidence intervals (CI).

RESULTS

Twenty-three patients were included (mean age 35 years old) who had been attending the outpatient clinic for about one year. The patients had a long history of recurrent UTIs. The most common pathogens identified during infections were: *Escherichia coli*, *Enterobacter species*, *Enterococcus species*, *Klebsiella species*, and *Proteus mirabilis*. All patients received antibiotic treatment, the most common antibiotics used were: amoxicillin/clavulanic acid (40%), ciprofloxacin (30%), and cotrimoxazole (20%) (**Figure 2**). In 16 (69.6%) patients, symptoms of RBC resolved after 8 months. In 5 (21.7%) patients after 8 months of HA treatment, urgency was reduced only by 30%. Therefore, it was decided to use combined therapy of HA and alpha blockers in this cohort group. There was 75% reduction in frequent urination at day and at night without urgency. Despite the use of above mentioned treatment, in 2 (8.7%) patients, RBC was still present and therefore the treatment was interrupted (**Figures 3 and 4**). The remaining cohort group of twenty one (91.3%) patients decided to continue the treatment and there are no side effects. The tolerability of HA and HA + alpha blockers treatment was good.

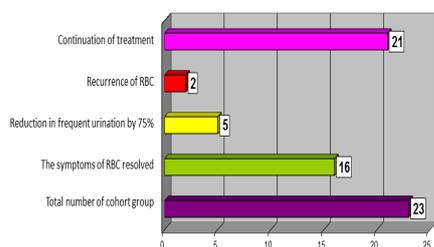


Figure 3. Number of patients continuing the treatment.

The meta-analysis showed a significant difference between the two groups within the results on UTI rates per patient per year (a group treated by HA and a group treated by combined therapy) (MD = 3.41, 95% CI: 4.33-2.49, $P < .00001$). It was reported outcomes on 24-h urinary frequency measured as 3-day voids (number of voids in 3 days), which were not significantly improved after therapy (MD = 2.53, 95% CI: 8.43-1.25, $P = .15$), but a significantly better PUF total score (MD = 7.17, 95% CI: 9.86-4.48, $P < .00001$) was detected in a group treated only by HA. Over the course of 9.5-month intravesical instillation with HA, 2 patients had a recurrence. In the extended follow-up (mean 12.5 months) none of the patients had a recurrence. Of patients, 21 (91.3%) were recurrence free after 9.5-month treatment. It was reported 95% decrease in the number of recurrences per year (rate of UTI: pre-treatment 4.1 ± 1.51 per patient/year vs. 0.2 ± 0.4 post-treatment, $P < .001$). Frequency score decreased from 7.56 ± 1.57 to 3.12 ± 2.11 ($P < .001$). Urgency score decreased from 7.21 ± 3.02 to 3.21 ± 2.23 ($P < .001$). Patient outcomes, expressed in terms of mean day- and night-time voids and mean pain scores showed no change in the average level of day-time voids, but did indicate an improvement in the average number of night-time voids. The percentage of patients improved, the magnitude and the duration of response were all measured by VAS, based on symptom response. Of patients, 91.3% reported an improvement ≥ 2 on the VAS score at the end of follow-up; 5% of patients experienced no change in symptoms. The absence of recurrent UTI was compared before and after HA instillations by plotting Kaplan-Meier curves for each period. Based on the follow-up for patients with or without recurrence the median time to recurrence after the first instillation of HA predicted by the model was 478 days; the median time to recurrence before HA was 83 days, which shows a significant difference ($P < .00001$).

DISCUSSION

This study demonstrates clear evidence that instilling HA into the bladder of a woman with a history of recurrent UTIs is feasible and well accepted by pa-

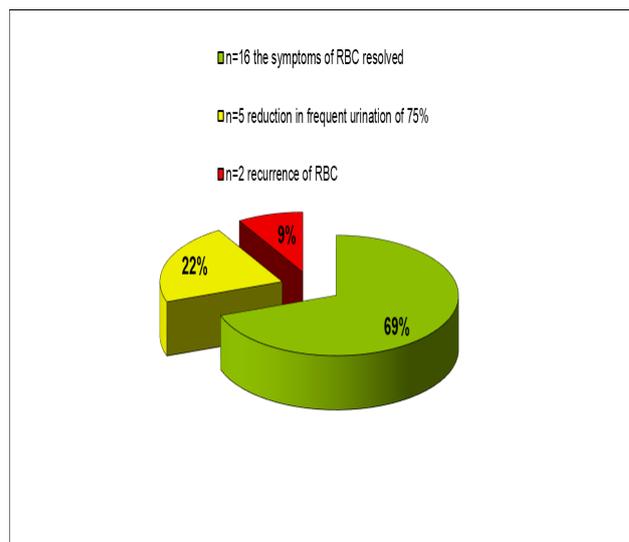


Figure 4. Results of recurrent bladder cystitis treatment by hyaluronic instillations.

tients, and significantly reduces the incidence of recurrent lower UTIs. In 13 of 17 patients, symptoms of RBC resolved. The phase of HA treatment lasted about 10 months, with weekly administrations for the first month followed by monthly treatments for 8 months. This regimen was based on pragmatic experience with HA therapy in patients with UTI at the authors' hospital, during which one patient had a recurrence UTI. However, the protective effect of HA was maintained even after direct treatment had stopped. Contemporary treatment options for women with a history of recurrent UTI usually include intermittent or prolonged antibiotic therapy, with variations in specific antibiotics, their dose, and duration of therapy.^(1,5) Alternatively, estrogen replacement therapy has been suggested as a strategy to decrease the incidence of recurrent UTIs in postmenopausal women, by reversing the changes in vaginal pH, and this is an example of an intervention not based on antibiotics.^(6,7) Raz and Stamm⁽⁷⁾ found that in women treated with intravaginal estriol cream there was a reduction in UTI recurrence and at 6 months $\approx 80\%$ of the treated patients remained infection-free. However no menopausal women were included in the present study and hence these patients would be ineligible for this antibiotic-free treatment. The third therapeutic approach targets bacterial adherence to bladder mucosa. The most successful have used cranberry juice, effective through its phenolic components.⁽⁸⁾ The principle of GAG substitution for preventing UTIs was shown experimentally in animals for heparin,⁽⁹⁾ and for sodium pentosan polysulphate.⁽¹⁰⁾ In the study of Sinanoglu and colleagues on comparison of intravesical administration of chondroitin sulfate and colchicine in rat protamine/lipopolysaccharide induced cystitis model, it was reported that colchicine may be an alternative to other treatment modalities for painful bladder conditions such as interstitial cystitis. Intravesical administration of colchicine decreased leucocyte and mast cell infiltration to the same extent of chondroitin sulfate in protamine sulfate and lipopolysaccharide induced bladder inflammation in rat.⁽¹¹⁾ We demonstrated that, bladder instillations of HA reduce

the incidence of recurrent UTI, 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.

CONCLUSION

The use of HA protects mucosa of urinary bladder and alleviates symptoms of infection. The intravesical instillations of HA seems to be an effective therapeutic alternative in patients with recurrent bacterial cystitis. However, it is a very expensive method of treatment.

CONFLICT OF INTEREST

None declared.

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