The use of intravesical hyaluronic acid for recurrent urinary tract infections in children: a case-series study

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Abstract

Background: This is the first study performed to evaluate the effects of intravesical hyaluronic acid (IHA) instillation on diminishing the frequency of recurrent urinary tract infections (UTIs) in children. Methods: Fifteen children (10 girls, 5 boys) with recurrent UTIs were divided into two groups as either complicated (group 1) (with accompanying disorders including vesicoureteral reflux or neurogenic bladder) or uncomplicated patients (group 2). After administration of weekly four sessions of IHA therapy the patients were followed-up monthly for 2 years and classified as responsive (complete/partial) or unresponsive to treatment. Results: 53.3% of the patients with recurrent UTIs were complicated. In group 1 (n = 8), complete and partial response rates were 62.5% (n = 5) and 25% (n = 2), respectively. There was no response in 12.5% (n = 1) of the cases in group 1. In group 2 (n = 7), complete and partial response rates were 71.4% (n = 5) and 14.3% (n = 1), respectively. In this group, 14.3% (n = 1) of the patients were found to be unresponsive to IHA treatment. No side effects were observed in any of the patients. Conclusions: IHA administration is considered as an effective treatment modality which significantly reduces the prevalence of or even provides complete recovery from recurrent UTIs in childhood. Therefore, it is believed that this approach can be used as a promising alternative to widespread use of antibiotics in this patient group.

Introduction

Urinary tract infections are frequently seen in children with the prevalence of 2–8% through all childhood age groups.1 There is predominance in girls after the first year of life and recurrence rate is approximately 12–30%.1–3 The risk of recurrence is increased in the patients with underlying vesicoureteral reflux (VUR) and bladder instability. Intermittent or long-term antibiotic therapies are traditionally being used in a large proportion of the patients in order to prevent recurrences and probable pyelonephritis-induced permanent kidney damage. However, these treatment modalities can induce several side effects and promote the development of resistant microorganisms.3,4 Therefore, there is a need for investigation of new alternative treatment approaches.

It is well-known that the glycosaminoglycan (GAG) layer of the bladder is essential for preventing bacterial adherence and it is protective against the toxic effects of the urine. For this reason, damage to the GAG layer is one of the mechanisms involved in the pathogenesis of urinary tract infections (UTIs).5 Escherichia coli is the leading microorganism identified in the urine cultures in most of the UTIs (60–80%);6 and it is demonstrated that the soluble virulence factors produced by E. coli can result in an additional damage the GAG layer.5

Hyaluronic acid is a mucopolysaccharide component of the body fluids and extracellular matrix of various tissues and it constitutes a major portion of the GAG layer of the bladder.4 Presence of hyaluronic acid in the uroepithelial basal membrane provides an anatomical barrier. Also, being the most important component of GAG layer, it also forms a functional epithelial barrier. Therefore, it is believed that administration of hyaluronic acid via intravesical route would replace the defective GAG layer.7

It was shown that intravesical hyaluronic acid (IHA) instillation resulted in a positive response in 30–73% of adult patients with interstitial cystitis/painful bladder syndrome (IC/PBS).8–13 This treatment modality is also used with success in patients with hemorrhagic cystitis that develop secondary to chemotherapy or radiotherapy.8,14–18 Similarly, it is reported that IHA administration resulted in a dramatic fall in the frequency of recurrent UTIs in adult women.5,8,12

To our knowledge, no studies exist in the literature evaluating the effects of IHA use in children with recurrent UTIs. For this purpose, herein we report the first results after IHA use in 15 children followed-up for recurrent UTIs with frequent episodes.
Materials and methods

Study population

Fifteen patients (10 girls, 5 boys) who were being followed-up in Gazi University, the divisions of both pediatric nephrology and surgery between January 2007 and December 2012 were enrolled. The patients who were attending for recurrent UTIs for at least 2 years prior the start of this study were recruited. The patients were selected among the ones with recurrent infections despite the history of the use of several treatment modalities including long-term antibiotic prophylaxis, anticholinergic drugs or non-invasive behavioral treatments for micturition or constipation. Written informed consents and local ethical committee approval were obtained before the start of the study.

Inclusion criteria

Criteria mentioned below were required for a definite UTI diagnosis: (i) Presence of urinary symptoms (dysuria, frequency, urgency, etc.), (ii) pyuria in the urine microscopy, (iii) a positive urine culture test. Only the cases with documented positive urine culture tests in each infection (growth of an uropathogen at \( \geq 10^5 \) and \( 10^4 \) colony forming units obtained by clean-catch midstream and catheterization, respectively)\(^1\) were enrolled. Also, in addition to a positive culture result, presence of fever, foul smell in urine and cloudy urine was essential to accept as a symptomatic UTI in patients performing clean intermittent catheterization due to their underlying pathologies.\(^2\) Recurrent UTI is defined as the occurrence of \( \geq 2 \) episodes of infection either presenting as acute pyelonephritis; or one episode as acute pyelonephritis plus one episode of cystitis/lower UTI; or three or more episodes of cystitis/lower UTI.\(^3\)

Exclusion criteria

Patients with non-adherence to treatment (the ones not taking their antibiotic prophylaxis or performing clean intermittent catheterization regularly), inappropriate toilet training for patients with normal sensation and presence of obstructive uropathy were excluded.

Retrospective phase of the study

The number of UTIs in the last 24 months before the initiation of IHA treatment was noted. Patients with accompanying disorders (such as VUR and neurogenic bladder) were accepted to be complicated and the study group was classified into two groups as either complicated (group 1) or uncomplicated patients (group 2).

Intravesical hyaluronic acid instillation

Before the initiation of each treatment session, it was made sure that the urine cultures were negative. The patients continued to take oral antibiotic prophylaxis which was trimethoprim-sulfamethoxazole (TMP-SMX) during the whole period of IHA instillations in all cases. A standard dose of HA was instilled into the bladder (Cythyal\(^5\) 50 mL/\(^4\) 40 mg). The dose was determined based on the recommendations of previous studies (that included pediatric cases), where IHA treatment was used for purposes other than UTIs.\(^15,16\) Before the instillation of the medication, a single-use temporary hydrophilic urinary catheter was inserted under sterile conditions in the outpatient clinic by the same technician and residual urine was drained. The patients were asked to retain the solution in their bladder for at least 1 h and then the urinary catheter was removed. Any side effects during and after the treatment were noted. If the patients consulted with urinary symptoms (such as dysuria and frequency) or fever and abdominal pain suggesting a UTI in between the IHA instillations, urinalysis and urine culture tests were rapidly performed in order to make a UTI diagnosis. In patients with no symptoms, it was also assured that urine cultures were negative before the initiation of each IHA treatment, as mentioned above. As a result, if the patients consulted with the evidence of new infections in between the sessions, then IHA instillation was delayed until the end of the treatment of this concurrent episode with antibiotics. Four standard weekly courses of IHA instillation were applied.

Prospective phase of the study

After the end of all sessions, the patients were called to control once monthly for the following 24 months and at each visit urinary cultures were repeated. The presence of UTIs was assessed and the number of infections was recorded. If the number of UTIs in the following 2 years after IHA administration sessions were less than 50% compared to the period prior to IHA therapy, the patient was accepted to have an partial response. If the urinary cultures remained sterile in each control, then a complete response was considered. The response rates of both groups were compared.

Statistical analysis

SPSS 15.0 software package (SPSS Inc., Chicago, IL) was used for statistical analysis and data are presented as frequencies and percentages. Chi-square test was used for the analysis of categorical variables. A \( p \)-value \(< 0.05 \) was considered statistically significant.

Results

Patient characteristics

The mean age of the patients was 11.0 ± 5.2 years (age range: 6.5–14 years). 53.3% of the patients with recurrent UTIs were complicated (\( n = 8 \)) (group 1) and there were uncomplicated UTIs in 46.7% of the patients (\( n = 7 \)) (group 2). The concomitant diseases of the patients in group 1 are given in Table 1.

Prior to the initiation of the IHA therapy, there were 0.98 and 0.79 UTIs per patient per month in patients with groups 1 and 2, respectively. A total of 83 infections were detected in group 1, whereas this number was 64 in group 2. Some of the infections presented as pyelonephritis (14 and 8 infections in groups 1 and 2, respectively). In this period, the most common isolated microorganism was \( E. \) coli in both groups constituting 61% and 49% of all infections in group 1 and 2, respectively (Table 2). The second most common bacterial agent was \( K. \) species. All of the microorganisms were

* Cythyal is former brandname of Hyacyst
resistant to TMP-SMX treatment. Standard antibiotic regimes were applied in all infections.

All cases were put on standard four weekly courses of IHA administration. The medication was well-tolerated in all patients and no side effects were observed during or after the treatment.

Results of group 1

No new UTIs emerged in the following the 24 months after IHA instillation in 62.5% \( (n = 5) \), whereas in 25% \( (n = 2) \), case 1 with operated grade V VUR and case 2 with neurogenic bladder there was a partial response characterized by a reduction from 1.03 to 0.41 infections per month before and after the treatment, respectively. When the patients with a partial response were further evaluated, it was detected that the UTI relapses started to occur after the end of the standard four sessions (after 101 and 142 days in cases 1 and 2, respectively; mean 121.5 days). However, there was no response in 12.5% \( (n = 1) \) of the cases despite the IHA courses. In this unresponsive patient (with underlying neurogenic bladder and VUR) frequent relapses were observed after the end of 4-week therapy, as well (Table 2). All of the infections were caused by \( E. \) \( \text{coli} \) or \( \text{Klebsiella} \) spp. and involved only the lower urinary tract.

Results of group 2

In the end of the 24 months, a complete response rate was 71.4% \( (n = 7) \), which was better than group 1. In 14.3% of the cases \( (n = 1) \), UTIs recurred at the 17th month of the follow-up period. Therefore, this patient was accepted to have a partial response. In 14.3% of the cases \( (n = 1) \), no response was achieved despite regular IHA administration. In this patient, UTIs recurred as early as following the second and fourth IHA instillations (Table 2). Again, all of the infections were caused by similar microorganisms and presented as a lower UTI.

Totally, a complete and a partial response was achieved in 66.7% \( (n = 10) \) and 20.0% \( (n = 3) \) of all patients, respectively. However, no optimal response was obtained in 13.3% \( (n = 2) \), Table 2).

Discussion

Contemporary management of UTIs involves administration of antibiotics but this treatment option is not without high percentage of recurrences or various side effects. In contrast to antibiotherapy, which aims at eradicating microorganisms, treatment with IHA targets the bacterial adherence to the bladder mucosa considering that both a damaged GAG layer facilitates bacterial adherence and consequent UTIs and the repair of this layer is with IHA is capable of preventing adherence.

As previously mentioned, IHA use was evaluated in different conditions including IC/PBS, hemorrhagic cystitis secondary to chemotherapy or radiotherapy and recurrent UTIs in adult patients. The overall complete response rate varied from 30% to 73% in patients with IC/PBS. In a current study, there were significant improvements in 61% of this group of patients. Moreover, in a 5-year follow-up study, 50% of patients showed complete bladder symptom remission without any additional therapy. Therefore, it was concluded that IHA instillation was a feasible treatment option for refractory IC/PBS patients who have failed to respond to previous treatment.

Intravesical hyaluronic acid treatment is also used with success in patients with hemorrhagic cystitis as a complication of chemotherapy, especially in conjunction with hematopoietic stem cell transplantation in adults. In a pediatric study by Cipe et al., it was reported that hemorrhagic cystitis resolved after two doses of IHA in a 7.5 year boy with hematopoietic stem cell transplantation.

The efficacy of IHA instillations in recurrent UTIs is also well-established in several adult studies. Constantinides et al. showed that there was a 70% recurrence-free rate in the end of 12.4 month follow-up in 40 women with recurrent UTIs with this treatment. In another study on 13 women with recurrent UTIs, a 51% complete response was achieved in the end of 21 month follow-up with four weekly then monthly IHA instillations.
In our study, we observed that there is an overall complete/partial response to IHA administration in 86.7% of the complicated and uncomplicated children with recurrent UTIs at the end of the 24-month follow-up. In one child in Group 2, the first UTI episode emerged as late as at the 17th month. As a result, our study provides a remarkably high response rate, which is similar or even superior to these previous adult studies. However, there are individual differences on the time needed for an optimal response after IHA therapy. Although standard four weekly sessions are sufficient for many, sometimes 6 or even 12 courses can be necessary. In our patient group, only four sessions were seemed to be sufficient in order to gain an adequate response in all patients.

No UTI episodes were observed over the 5-month IHA therapy in 40 adult women with recurrent UTIs and this therapeutic approach was reported to be protective against UTIs during direct treatment period. In our study, however, UTI episodes recurred as early as after the second IHA instillation in a single patient in Group 2.

A single patient in Group 1 underwent bladder augmentation by enterocystoplasty. This patient was one of the complete responders to IHA treatment. It was shown that hyaluronic acid was synthesized throughout the course of bladder wound healing and regeneration in small intestinal submucosa-augmented rat bladder, and it was proposed that exogenous hyaluronic acid delivery could improve regenerative responses. Therefore, although no previous reports exist on the use of IHA therapy in patients with bladder augmentation; we may speculate that this treatment modality could have beneficial effects on bladder regeneration as well as being protective against UTIs.

Two patients in group 1 had grade V VUR during IHA treatment. These patients had also non-compliant bladders with a reduced capacity which exposed them toward increased intravesical pressures. As a result, the surgical correction of VUR was not indicated in these cases and IHA instillations were tried in order to prevent the frequent UTI episodes. The treatment was applied to an emptied bladder and the amount of the solution (40 mL) was still under the bladder capacity. Therefore, we did not expect the medication to reach up to the renal pelvis. One of those patients was a complete responder; however, frequent infections emerged in the other one right after the end of four-weekly sessions. Again, no reports were present in the literature concerning the use of IHA in patients with apparent VUR; we may consider that this approach could be useful in selected cases with special conditions.

Up to date, no systemic side effects were reported after IHA use. The most common side effect was local pain due to catheterization. Nevertheless, we did not observe any adverse effects either during or after IHA administration. Additionally, all the patients were in good cooperation and the procedure of catheterization was tolerated even in the patients with normal sensation. In our study, the UTIs occurred in all patients after the cessation of IHA use except one. In this patient, the infections developed after the second and fourth courses. As the instillations were made under sterile conditions by the same experienced personnel in each session, we believe that these infections were induced by factors other than the catheterization itself.

During IHA instillations, it was ensured that the patients voiding spontaneously kept their daily routines for micturition or defecation. No behavioral modifications were made in order to eliminate their contribution on reduction of the UTI frequencies. For this reason, we believe that the high response rates to the IHA treatment were not influenced by these factors.

Our study has its limitations, including the small sample size and the lack of a placebo-control group. However, considering the past history of our patients, we believe that the number and the frequency of UTIs would be much higher if the some of the patients remained only on antibiotic prophylaxis. We believe that larger patient numbers and longer follow-up duration are needed to confirm our results.

Conclusions

We want to emphasize that the data of our study are the first to report about the efficacy of IHA treatment in children. We observed that IHA administration is an effective treatment modality which significantly reduces the prevalence of or even provides complete recovery from recurrent UTIs in children with/without complications. We believe that this approach can be a promising alternative to the widespread use antibiotics in this patient group.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References


