Review – Female Urology – Incontinence

Hyaluronic Acid: An Effective Alternative Treatment of Interstitial Cystitis, Recurrent Urinary Tract Infections, and Hemorrhagic Cystitis?

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**Abstract**

**Objectives:** Hyaluronic acid is a protective barrier of the urothelium. A damaged glycosaminoglycan layer may increase the possibility of bacterial adherence and infection. This damage is proposed to be a causative factor in the development of interstitial cystitis, common urinary tract infections, and hemorrhagic cystitis due to posthematopoietic stem cell transplantation. The aim of this article was to review the available data regarding the use of hyaluronic acid as an alternative treatment of the above-mentioned conditions.

**Methods:** Articles relevant to our review that were archived by September 2006 were retrieved from PubMed.

**Results:** Nine relevant studies were identified and evaluated. Hyaluronic acid was administered intravesically at a dose of 40 mg every week for 4–6 wk; patients with noted improvement received two additional monthly doses. Short-term responses of patients with interstitial cystitis, hemorrhagic cystitis, and recurrent urinary tract infections were 30–73% (7 studies), 71% (1 study), and 100% (1 study), respectively. The treatment was well tolerated except for occasional development of bacterial cystitis. The cost of each intravesical installation of hyaluronic acid is 120 UK pounds (excluding the cost of the urinary catheterization).

**Conclusions:** The available clinical data regarding the effectiveness of hyaluronic acid as a potential treatment of patients with interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis are limited. There is need for randomized controlled trials for further investigation of this important therapeutics question; these clinical trials should be disease-specific, blinded, and controlled, and of a sufficient number of patients. Until such studies are available, intravesical instillation of hyaluronic acid cannot be unquestionably endorsed for use for the aforementioned diseases.

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1. Introduction

Hyaluronic acid is a major mucopolysaccharide found widely in the connective, epithelial, and neural tissues. It is one of the main components of the extracellular matrix that contributes significantly to cell proliferation and migration, and may also be involved in the progression and migration of some malignant tumors [1]. Hyaluronic acid in the urothelium constitutes a protective barrier [2,3]. It exhibits a variety of properties that may contribute to its prophylactic mechanism [4–10]. Among them are (1) inhibition of adherence of immune complexes to polymorphonuclear cells; (2) marked inhibition of leukocyte migration and aggregation, depending on viscosity; (3) regulation of fibroblast and endothelial cell proliferation; and (4) enhancement of connective tissue healing. A damaged glycosaminoglycan layer may lead to direct exposure of epithelial cells to components of urine; for this reason the possibility of bacterial adherence and infection increases [8–10]. This damage is proposed to be a causative factor in the development of interstitial cystitis [11], common urinary tract infections (UTIs) [12], and hemorrhagic cystitis due to posthematopoietic stem cell transplantation [2].

Hyaluronic acid is used in clinical practice in the treatment of patients with osteoarthritis (by intraarticular injections) [13] or asthma [14]; in certain ophthalmologic [15] and otologic [16] operations; in cosmetic regeneration and reconstruction tissue [17]; and in cystitis [2,3] and vesicoureteral reflux [18]. The aim of this article is to critically review the available evidence regarding the use of hyaluronic acid as an alternative treatment of interstitial cystitis, recurrent urinary tract infections, and hemorrhagic cystitis.

2. Interstitial cystitis

Interstitial cystitis is a chronic disease characterized by urinary frequency, bladder pain, nocturia, and urgency. It usually affects women [19]. The prevalence of interstitial cystitis ranges from 10 up to 510 cases per 100,000 population [20,21]. Interstitial cystitis is frequently a diagnosis of exclusion. Many etiologic factors [20,22–24] have been suggested for this condition, including autoimmune response, mast cell activation, neuropathic changes, occult infection, toxic substances in the urine, and a primary defect in the glycosaminoglycan layer of the bladder mucosa. It has been suggested that a defect in the glycosaminoglycan layer allows access of different components of urine, such as ions, microorganisms, and toxic molecules, to the bladder urothelium [25,26], and urinary hyaluronic acid levels correlate with interstitial cystitis [27]. There is no specific treatment for interstitial cystitis because of its uncertain cause and pathogenesis. Tricyclic antidepressants, anti-inflammatory drugs, and a wide range of epithelial-coating techniques including the use of heparin, sodium pentosan polysulfate, and hyaluronic acid have been used [20,22,26,28–31]. Hyaluronic acid is considered a good candidate for glycosaminoglycan substitution. In addition, heparin and dimethyl sulfoxide are often used in patients with interstitial cystitis. These agents’ actions are not quite clear, but they supposedly act via their anti-inflammatory effects. Other agents for intravesical treatment are Bacillus Calmette-Guerin vaccine and botulinum toxin, and some recent studies have pointed to resiniferatoxin and RDP58 [32].

3. Urinary tract infections

UTI is a very common type of bacterial infection, especially in women. Not every patient with UTI has symptoms. When symptoms are present, patients feel urgency, frequency, nocturnition with small voidal volume, bladder or urethra pain during urination, suprapubic discomfort, and sometimes fullness in the rectum. Presence of fever, pain in the back or side below the ribs, nausea, and vomiting indicates kidney infection [33]. Management of UTIs involves administration of antibiotics, but a high percentage of recurrent infections still occur [12]. Contemporary treatment options could also be estrogen replacement therapy [12], use of cranberry juice [34] or probiotics [35], as well as glycosaminoglycan substitution by using heparin, sodium pentosan polysulfate, or hyaluronic acid [12].

4. Hemorrhagic cystitis

Hemorrhagic cystitis is a relatively common (incidence: 7–68%) and potentially severe complication of high-dose chemoradiotherapy, especially in conjunction with hematopoietic stem cell transplantation. There is no established effective treatment for this type of cystitis [2].

5. Literature search

Using the online PubMed database, we searched for articles relevant to our study that were archived by
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>Treatment of cystitis</th>
<th>Treatment scheme</th>
<th>Results</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miodosky et al</td>
<td>2006</td>
<td>7</td>
<td></td>
<td>Hemorrhagic cystitis after HSCT</td>
<td>4 weekly doses plus monthly doses</td>
<td>5/7 complete response at a median of 12 d (range: 7–23) 1/7 partial response 1/7 no response (death from septic shock) No local or systemic side effects</td>
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<tr>
<td>Daha et al</td>
<td>2005</td>
<td>48</td>
<td>Mean: 54 (range: 22–82)</td>
<td>Interstitial cystitis (but a bladder capacity of &gt;350 cc on a 0.9% NaCl cystometry was accepted)</td>
<td>10 weekly doses</td>
<td>41/48 improvement 27/32 (84%) in group 1 14/16 (87%) in group 2</td>
<td>6 mo (3–16 mo)</td>
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<tr>
<td>Gupta et al</td>
<td>2005</td>
<td>38</td>
<td></td>
<td>Interstitial cystitis</td>
<td>6 weekly doses and choice of continuing monthly in responders</td>
<td>20/36 improvement (55%) after 6 doses (74% of PST-positive patients and 23% of PST-negative patients) 3 patients referred pain 3 patients developed UTI Current cost: UK 120 pounds, excluding nursing and day-surgical unit costs Inconvenience of weekly visits Loss of working time and earnings</td>
<td></td>
</tr>
<tr>
<td>Kallestrup et al</td>
<td>2005</td>
<td>20</td>
<td>34–80</td>
<td>Interstitial cystitis</td>
<td>4 weekly doses plus 2 monthly doses plus choice of continuing monthly in responders</td>
<td>40% decrease in nocturia 30% decrease in pain Decrease in analgesic use 13/20 responders (65%) 6/20 lack of response 1/20 withdrawn due to cystectomy Well tolerated by all patients 5/20 bacterial cystitis due to repeated catheterisation No correlation between efficacy and time of retained solution in the bladder After 3 yr: 4/13 complete responders, 7/13 partial responders 2/13 other diseases during follow-up</td>
<td>3 yr</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Patients</td>
<td>Condition</td>
<td>Dosing Schedule</td>
<td>Results</td>
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<tr>
<td>Constantinides et al [12]</td>
<td>2004</td>
<td>40</td>
<td>Recurrent UTIs</td>
<td>4 weekly doses plus 4 monthly doses</td>
<td>40/40: recurrence free during 5 mo, 28/40 (70%): recurrence free during follow-up, Median time of recurrence 498 d (compared with 96 d before treatment), Excellent tolerability, 9/40 mild bladder irritation, 40/40 compliance</td>
<td></td>
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<tr>
<td>Leppilahti et al [38]</td>
<td>2002</td>
<td>11</td>
<td>Interstitial cystitis</td>
<td>4 weekly doses</td>
<td>8/11 responders, 3/8 long-term responders, 5/8 short-term responders, Responders: 75% decrease in pain, Long-term responders: 40% decrease in frequency, Short-term responders: 26% decrease in frequency</td>
<td></td>
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</tr>
<tr>
<td>Nordling et al [26]</td>
<td>2001</td>
<td>20</td>
<td>Interstitial cystitis</td>
<td>4 weekly doses plus monthly doses for 2 mo</td>
<td>1/20 withdrawn due to cystectomy, 7/19 responders, 6/19 nonresponders, 4/19 recovered during treatment, 2/19 stopped before follow-up</td>
<td></td>
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<td>Morales et al [3]</td>
<td>1997</td>
<td>25</td>
<td>Interstitial cystitis</td>
<td>4 weekly doses plus monthly doses for 1 yr responders</td>
<td>16% complete response by week 4, 25% complete response by week 24, 56% response (complete or partial) for week 4, 71% response (complete or partial) by week 12, 71% response (complete or partial) till week 20, Decrease beyond rate 24 weeks, No significant toxicity, 1/25 withdrew because of exacerbation of bladder irritability</td>
<td></td>
<td></td>
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<tr>
<td>Porru et al [39]</td>
<td>1997</td>
<td>10</td>
<td>Interstitial cystitis</td>
<td>6 weekly doses plus monthly doses</td>
<td>30% response in 6 weeks, 30% response in 24 weeks, No significant local or general side effects, Well tolerated</td>
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</table>

HSCT = hematopoietic stem cell transplant; Cmax = maximum plasma concentration; PST = potassium sensitivity test; UK = United Kingdom; UTI = urinary tract infection.

* These three studies were randomised controlled trials. The studies by Gupta et al and Porru et al were double-blinded, placebo-controlled trials. Porru et al did not report the method used for double-blinding, while Gupta et al reported that the pharmacy supplied the medications in bottles labeled A and B to ensure double-blinding.
September 2006. The key words we used in our literature searches were hyaluronic acid, hyaluronate, cystitis.

6. Study selection and evaluation

The focus of our study was in articles that described the role of hyaluronic acid in the prevention or treatment of different types of cystitis. Only English language studies were included in this review. We identified a total of 27 potentially relevant articles. From these, 15 were excluded because they did not focus on the topic of our study. In addition, 3 articles were excluded because they were animal studies. As a result 9 studies remained that met the inclusion criteria of our review. Relevant data were extracted from each study and tabulated. The information retrieved included the number of patients, the route of hyaluronic acid administration, the results (positive or negative), and the follow-up of each study.

7. Critical review of the available evidence

From our literature search we found seven studies [19,20,22,26,36–39] that investigated the role of hyaluronic acid in the treatment of patients with interstitial cystitis (total number of patients: 172), one study [12] regarding the treatment of patients with recurrent UTIs (total number of patients: 40), and one study [2] regarding the treatment of patients with hemorrhagic cystitis (total number of patients: 7). In Table 1 we present the data extracted from the relevant reviewed studies.

Patients received four to six weekly intravesical installations of hyaluronic acid at a dose of 40 mg in a volume of 50 ml of phosphate-buffered saline. Responders then received monthly doses. The intravesical installation was performed with the use of a catheter, under sterile conditions, after removal of residual urine. The patients retained the intravesical hyaluronic acid for a minimum time of 30 min [2,12,19,20,22,26,36–39]. Kallestrup et al [20] found no correlation between the retention time in the bladder (range: 28–155 min) and the effectiveness of hyaluronic acid. Gupta et al [21,37] and Daha et al [19] proposed the use of a positive potassium sensitivity test before the use of hyaluronic acid to identify patients with predominant epithelial dysfunction, who are thought to be better responders to this treatment.

The available data suggest that the total short-term response of patients with interstitial cystitis is from 30% [39] up to 73% [38], and the long-term (3 yr) response of such patients could reach 55% [20]. Miodosky et al [1] reported that the total response to the treatment in patients with hemorrhagic cystitis is 71%. Constantinides et al [12] found that, in patients with recurrent UTIs, intravesical treatment with hyaluronic acid was associated with absence of recurrence in 100% and 70% of patients during 5-mo and 1-yr follow-up, respectively.

8. Adverse events

The use of hyaluronic acid is usually well tolerated [2,12,19,20,22,26,36–39]; for this reason high compliance with the treatment was achieved in the reviewed studies and is also expected in clinical practice. No serious local or systemic adverse events were mentioned in the reviewed studies, except mild bladder irritation. A reported adverse event was bacterial cystitis that was most likely related to the repeated bladder irritation rather than the therapeutic agent itself.

9. Cost

The cost of each intravesical installation of hyaluronic acid is 120 UK pounds. This figure does not include the cost of the urinary catheterization, the cost of the services of the health care personnel, and the loss of working time and earnings due to the need for intravesical administration of the drug [22]. For these reasons, we believe that cost-effectiveness analyses regarding the use of hyaluronic acid in patients with the examined diseases should be performed.

10. Limitations in the interpretation of the available evidence

The major issue in interpreting the available evidence regarding the effectiveness and safety of hyaluronic acid for the examined diseases is that there are only limited relevant published data. Thus, one cannot make definitive statements on the reviewed topics. In addition, an important limitation of the evaluated studies is the fact that only three of the nine reviewed studies were randomized controlled trials. It should be mentioned that, in two of these three trials, hyaluronic acid was compared with placebo, while in one of these three trials women were stratified by bladder capacity or...
potassium chloride test, and pre- and protreatment analyses were done. While this methodology has several advantages, we should emphasize that this new therapeutic modality was not compared with other commonly used therapeutic options in patients with the examined diseases. In addition, the statistical significance and the cut-off of significance were reported in only six of the reviewed articles, the number of dropouts from the study and the reason that led participants to dropout were reported in three articles, and specific information regarding adverse events of intravesical treatment with hyaluronic acid in were reported in six articles. Finally, it should be emphasized that intravesical hyaluronic acid is not an approved treatment for the examined indications in the United States and United Kingdom at the time of writing of this article (November 2006).

11. Conclusions

There is a scarcity of data regarding the mode of action of hyaluronic acid as well as its effectiveness for the examined diseases in this article. The limited available evidence from the reviewed studies suggests that hyaluronic acid may be considered for further studies, including randomized controlled trials with adequate power. These clinical trials should be disease-specific, blinded, and controlled, and include a sufficient number of patients to answer the important relevant study questions. Until such studies are available, the effectiveness of intravesical instillation of hyaluronic acid as a potential alternative treatment of interstitial cystitis, recurrent UTIs, and hemorrhagic cystitis remains unknown.

Conflicts of interest

There are no financial or other relationships that might lead to a conflict of interest.

Funding: None.

References


[26] Nordling J, Jorgensen S, Kallestrup E. Cystistat for the treatment of interstitial cystitis, recurrent urinary tract infection, or hemorrhagic cystitis. The hyaluronic acid solution is instilled directly into the bladder, and repeated instillations are necessary. An effective treatment for any of these clinical entities could be enthusiastically embraced. However, these syndromes are characterized by remission and relapse and the short-term course for any given patient cannot be predicted.


Editorial Comment on: Hyaluronic Acid: An Effective Alternative Treatment of Interstitial Cystitis, Recurrent Urinary Tract Infections, and Hemorrhagic Cystitis?

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In this issue, Iavazzo et al review studies evaluating the use of intravesical instillation of hyaluronic acid, a glucosaminoglycan replacement therapy, for management of interstitial cystitis, recurrent urinary tract infection, or hemorrhagic cystitis [1]. The hyaluronic acid solution is instilled directly into the bladder, and repeated instillations are necessary. An effective treatment for any of these clinical entities could be enthusiastically embraced. However, these syndromes are characterized by remission and relapse and the short-term course for any given patient cannot be predicted.

Unfortunately, as the review concludes, available studies are limited in number and quality. The authors identified only nine studies: one involving 40 patients with urinary infection, one examining 5 patients with hemorrhagic cystitis, and seven studies on interstitial cystitis. They identify flaws, including statistical methodology and reporting of adverse effects. Only three studies were randomized trials, one of which used two different regimens of hyaluronic acid. Although the authors suggest two studies were double-blind and placebo-controlled, both of these, on inspection, are uncontrolled “before and after” studies [2,3]. Thus, the knowledge base is insufficient to support any conclusion about the role of hyaluronic acid bladder instillations.

Placebo-controlled trials are essential to assess the efficacy of any therapy for chronic diseases without an accepted optimal treatment and with an unpredictable clinical course. For interstitial cystitis and recurrent urinary tract infection, prospective, randomized, placebo-controlled trials of potential therapies have repeatedly been published; such studies are certainly feasible. It is unfortunate that any potentially effective therapy has not been evaluated in appropriate clinical trials and unfair to promote interventions to patients who suffer from distressing illnesses before efficacy is
documented. We await, with interest, publication of well-conducted, randomized, placebo-controlled trials evaluating the use of intravesical hyaluronic acid for any urologic syndrome.

References


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