The Clinical Effectiveness of Intravesical Sodium Hyaluronate (Cystistat®) in Patients with Interstitial Cystitis/Painful Bladder Syndrome and Recurrent Urinary Tract Infections

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Key Words

Hyaluronic acid • Painful bladder syndrome •
Recurrent urinary tract infection

Abstract

Objective: Painful bladder syndrome/interstitial cystitis (PBS/IC) and recurrent urinary tract infections (UTI) are clinically challenging conditions to manage in patients. We evaluate the clinical use of intravesical sodium hyaluronate (Cystistat®) in both these patient groups who have completed treatment. **Patients and Methods:** Thirteen patients with recurrent UTIs (Group I) and 8 patients with PBS/IC (Group II) received intravesical sodium hyaluronate (Cystistat®). Pre-installation demographic parameters were statically comparable in both groups. The mean age of presentation was 54.6 years in Group I and 57.5 years in Group II ($p = 0.9$). All 13 patients in Group I were on low dose antibiotics. The mean number of installations completed in both groups was 9 (range 4–21). **Results:** Data was collected prospectively using a standard pre- and post-treatment questioner with the pelvic pain and urinary/frequency patient symptom scale. At a mean follow-up of 21 months a significant improvement in bladder pain ($p = 0.05$), daytime frequency ($p = 0.03$) and quality of life ($p = 0.02$) was noted in patients in Group I. Two

patients had breakthrough UTIs during treatment. Within Group I, 7 (53%) patients responded well to treatment. Patients in Group II had a significant improvement in bladder pain ($p = 0.02$), urgency ($p = 0.01$), nocturia ($p = 0.01$) and quality of life ($p = 0.04$). Within Group II, 6 patients (75%) responded to treatment. **Conclusion:** Intravesical sodium hyaluronate (Cystistat®) can be used with minimal side effects and good compliance in both groups of patients with PBS and recurrent UTIs. Longer follow-up and larger patient numbers in both groups will be required to confirm the long-term efficacy of these two clinically challenging groups of patients.

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Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) and recurrent urinary tract infections (UTIs) are both challenging conditions to treat. Nearly half of all women will have a UTI in their lifetime and a third before they are 24 years old [1, 2, 11]. Up to 35% of UTIs will recur within

Table 1. Preinstallations parameters (Mann Whitney U test)

	Group I (n = 13)	Group II (n = 8)	p
Male : Female	3 : 10	2 : 6	
Current age (years)	54.69 ± 4.901	57.50 ± 4.641	0.9711
Age at initial presentation (years)	46.38 ± 4.763	53.00 ± 4.444	0.4688
Urodynamic findings	DO (n=4), N (n=8), Hypo (n=1)	DO (n=3), N (n=5)	
Previous treatments			
Overdistentions	1	7	
Urethral dilatations	4	0	0.5866
Botox	1	1	0.3627
Anticholinergics	3	3	1.0000
Patients on antibiotics, n	13 (100%)	0 (0%)	0.0798
Preinstallation bladder volume (ml)	247.3 ± 36.82	198.8 ± 16.55	
Preinstallation pain score (N/10)	7.769 ± 0.3782	8.375 ± 0.3750	0.0535
Preinstallation daytime frequency (N)	11.38 ± 1.546	11.88 ± 1.856	0.9710
Preinstallation urgency (N/10)	6.538 ± 0.8595	8.875 ± 0.6391	0.9421
Preinstallation continence (N)	C (n=10), IC (n=3)	C (n=8), IC (n=0)	
Preinstallation nocturia (N)	4.000 ± 0.5883	1.625 ± 0.3750	0.6120
Preinstallation QoL	2.154 ± 0.3553	2.125 ± 0.5806	0.5613
Number of installations	9.385 ± 1.567	9.000 ± 1.803	
Number of patients having had completed treatment	Completed (10), ongoing (3)	Completed (7), ongoing (1)	
Duration of treatment (weeks)	23.10 ± 6.626	22.46 ± 9.788	
Duration of follow-up from treatment (months)	20.68 ± 6.363	14.46 ± 7.382	

DO = Detrusor overactivity; Hypo = hypotonic bladder; C = Continent; IC = Incontinent.

3-6 months [3, 4, 11]. Recurrent UTI is defined as 2 uncomplicated UTIs in 6 months or, more traditionally, as 3 positive cultures within the preceding 12 months [5, 6]. The high incidence of this condition is associated with a high financial burden internationally [1, 4, 11]. The prevalence of PBS/IC has been quoted as 10–530/100,000 [7, 8, 17]; the wide prevalence reflects the lack of consensus in what constitutes PBS/IC [7, 20]. The morbidity resulting from both conditions is significant to patients and has led to increasing interest and research to understand the pathogenesis and treatment options of the causes of these conditions and ways of treating them.

It is postulated that a deficiency in the protective lining of the bladder epithelium is a common pathway in the development of PBS/IC, UTIs and bladder carcinoma [9, 13, 20]. Glycosaminoglycan is an important component of this protective lining and various coating techniques have been used to try and repair this layer with variable result. A review of available literature by Iavazzo et al. [14] showed a positive response ranging from 30 [15] to 73% [16] following intravesical instillation of hyaluronic acid (HA) in patients with PBS. In their pioneering work, Constantinides et al. [13] instilled intravesical HA in 40

women with recurrent UTIs and 70% were recurrence-free at a mean follow-up of 12.4 months. Since then, there have only been 2 other studies evaluating the use of HA in recurrent UTIs both of which showed decrease in UTI rate per person per year and prolongation of mean time to recurrence [21, 22]. We present our initial results in the use of 40 mg Intravesical sodium hyaluronate (Cystistat®) in patients with PBS/IC and recurrent UTIs who have completed treatment.

Patients and Methods

Twenty-one patients were recruited prospectively into this case review study, 13 of them had recurrent UTIs (Group I) and 8 had PBS/IC as per International Continence Society criteria (Group II). Patients in both groups were comparable in terms of age and sex distribution (table 1). The mean age at presentation was 46 years (range 15–69 years) in Group I and 53 years (range 35–70 years) in Group II. The male to female ratios for the groups were 3:10 (Group I) and 2:6 (Group II). All patients recruited in Group II fulfilled the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria for PBS/IC. The patients had bladder pain syndrome diagnosed on the basis of pain, pressure or discomfort associated with the urinary bladder, accompanied by

Table 2. Symptom response in Group I patients with recurrent UTIs receiving intravesical sodium hyaluronate (Cystistat®)

UTIs	Pre-instillation	Post-instillation	p
Number of patients on antibiotics	13 (100%)	2 (15%)	
Bladder volume (ml)	247.30 ± 36.82	321.50 ± 38.64	0.7972
Pain score (N/10)	7.77 ± 0.38	3.39 ± 0.75	0.0005*
Frequency (N)	11.38 ± 1.55	7.92 ± 1.56	0.0354*
Urgency (N/10)	6.54 ± 0.86	4.15 ± 0.87	0.0680
Nocturia (N)	4.00 ± 0.59	4.00 ± 0.96	0.9181
QoL	2.15 ± 0.36	5.39 ± 0.90	0.0207*
Responder (n=7)			53%
Non responders (n=6)		1 SPC, 3 Ileal conduits , 2 on antibiotics	47%

* Statistically significant.

at least one other symptom, such as daytime and/or night-time increased urinary frequency. Patients in Group II had a cystoscopy, hydrodistention and biopsy to confirm the diagnosis.

All patients were given pre- and post-treatment “The Pelvic Pain and Urinary/Frequency (PUF) Patient Symptom Scale questionnaires” to assess the degree of their symptoms. All patients had urodynamic studies in both groups to exclude any pathological cause for symptoms. Four patients (30.8%) in Group I had evidence of detrusor overactivity (DOA) on urodynamics and the remaining patients (n = 9) had a normal urodynamic assessment. All patients in Group II had urodynamic assessments confirming the absence of DOA and additional parameters fulfilling the NIDDK inclusion criteria. Pain was assessed using the visual analogue scale and quality of life (QoL) was assessed.

Patients in both groups received intravesical sodium hyaluronate (Cystistat®) and retained the drug for a minimum of 30 minutes as per the manufacturer recommendation. We compared these 2 groups to assess the overall response instead of presenting the data of each individual group.

The pre-instillation demographic parameters were statistically comparable in both groups (table 1): bladder volumes were 247.30 ± 36.82 ml in Group I and 198.80 ± 16.55 ml in Group II (p = 0.5866); pain scores were 7.77 ± 0.38 in Group I and 8.38 ± 0.38 in Group II (p = 0.3627); the frequency scores were 11.38 ± 1.55 in Group I and 11.88 ± 1.86 in Group II (p = 1.0000); the nocturia scores were 4.00 ± 0.59 in Group I and 1.63 ± 0.38 in Group II (p = 0.0535); the urgency scores were 6.54 ± 0.86 in Group I and 8.88 ± 0.64 in Group II (p = 0.0798); the QoL scores were 2.15 ± 0.36 in Group I and 2.13 ± 0.58 in Group II (p = 0.9710). All 13 patients in Group I were on low dose antibiotics; none of the patients in Group II were on antibiotics.

All patients in Group II fulfilled the International Continence Society criteria for PBS/IC. Patients within this group had been treated with different treatment options including cysto-overdistention and transurethral resection of bladder ulcers with no symptomatic response. Four patients had a pathological diagnosis of PBS/IC on the basis of bladder biopsies confirming features of inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Patients in both groups received intravesical sodium hyaluronate (Cystistat®) – 50 ml vial of 40 mg was instilled into an empty bladder and patients were asked to hold this for at least 30 minutes. This was repeated weekly for 4 weeks, and then, subsequently on monthly basis. The mean number of instillations completed in both groups was 9 (range 4–21).

Results

Data was collected prospectively using the pelvic pain and urinary/frequency patient symptom scale questionnaires both pre- and post-treatment and visual analogue scale for pain. At a mean follow-up of 21 months a significant improvement in bladder pain (p = 0.0005), daytime frequency (p = 0.0354) and QoL (p = 0.0207) was noted in Group I patients. Two patients (15%) had breakthrough UTIs during treatment.

On the completion of treatment, no statistical significance was observed for the following parameters (table 2): bladder volume (p = 0.7972), urgency (p = 0.0680) and nocturia (p = 0.9181). In comparison, a significant statistical difference (Mann Whitney U test p value ≤ 0.05) was seen in pain reduction on the visual analogue scale from 7.77 ± 0.38 (pre-instillation) to 3.39 ± 0.75 (post-instillation). Daytime frequency reduced from 11.38 ± 1.55 to 7.92 ± 1.55 (p = 0.0354) and QoL improved from 2.15 ± 0.36 to 5.39 ± 0.90 (p = 0.0207) after treatment. The duration of treatment was 23.10 ± 6.63 weeks and patients were followed-up for 20.68 ± 6.36 months after treatment. There were 7 responders (53%) and 6 non-responders (47%). Amongst the non-responders 3 patients (50%) continued to be on rotating low dose prophylactic antibiotics. Two patients with DOA and recurrent UTIs

Table 3. Symptom response in Group II patients with PBS receiving intravesical sodium hyaluronate (Cystistat®)

PBS	Pre-instillation	Post-instillation	p
Number of patients on antibiotics	0 (0%)	0 (0%)	
Bladder volume (ml)	198.80 ± 16.55	276.30 ± 44.84	0.2345
Pain score (N/10)	8.38 ± 0.38	4.00 ± 1.13	0.0207*
Frequency (N)	11.88 ± 1.86	8.00 ± 0.91	0.3282
Urgency (N/10)	8.88 ± 0.64	5.25 ± 0.94	0.0148*
Nocturia (N)	2.25 ± 0.49	1.63 ± 0.38	0.0148*
QoL	2.13 ± 0.58	5.25 ± 1.18	0.0499*
Responders (n=6)		6	75%
Non-responders (n=2)		ileal conduit (1), Botox (1)	25%

* Statistically significant.

have had ileal conduits formed and one patient is currently being counseled for an ileal conduit.

Patients in Group II had a significant improvement in bladder pain ($p = 0.0207$), urgency ($p = 0.0148$), nocturia ($p = 0.0148$) and QoL ($p = 0.0499$) at 15 months follow-up. Six patients (75%) responded completely to intravesical sodium hyaluronate (Cystistat®) and required no further treatment.

Within Group II, no observation in any statistical significance was noted with volume of bladder ($p = 0.2345$) and daytime frequency ($p = 0.3282$) following treatment (table 3). Patients noted a significance in visual analogue scale reduction from 8.38 ± 0.38 to 4.00 ± 1.13 ($p = 0.0207$), urgency improved from 8.88 ± 0.64 to 5.25 ± 0.94 ($p = 0.0148$) and nocturia from 2.25 ± 0.49 to 1.63 ± 0.38 ($p = 0.0148$). There was statistical significance in QoL, which improved from 2.13 ± 0.58 to 5.25 ± 1.18 ($p = 0.0499$). The duration of treatment was 22.46 ± 9.79 weeks and follow-up continued for 14.46 ± 7.38 months after treatment. There were 6 responders (75%) and 2 non-responders (25%). One of the non-responders had ileal conduit surgery and the other had intravesical Botox injection.

Discussion

In clinical urological practice patients with recurrent UTIs and PBS/IC can be challenging to manage. As per the European Urological Association PBS/IC describes a chronic, distressing bladder condition [24], the so-called ulcer can be a typical cystoscopic finding in 10–50%

of IC patients. Various medical and surgical treatments have been described in the literature for this condition with variable results [7, 13–15, 19]. They include oral hydroxyzine, amitriptyline, pentosan, prostaglandins, cyclosporin A, duloxetine, oxybutynin, intravesical pentosan, botox, heparin, anesthetics, bacillus Calmette-Guerin, choindroitin sulphate, vanilloids, dimethyl sulphoxide and HA. Operative interventions have included bladder distension, sacral neuromodulation, epidural pain pumps, transurethral resection coagulation and laser, and reconstructive surgical treatment [6, 19].

Here, we define PBS/IC as a debilitating condition characterized by bladder pain, urgency, and urinary frequency for at least 6 months in duration without an identifiable cause. Its prevalence has been quoted as 10–530/100,000 [7, 8, 17]; again a reflection of our poor understanding of this condition. It is a diagnosis of exclusion with an average delay of 4 years before a diagnosis is established [22].

Our patients were selected based on the NIDDK criteria and after an average of 9 instillations of intravesical HA over 22 weeks, we observed significant improvement in pain, urgency, nocturia and QoL over a 14-month follow-up period. Two patients (25%) did not benefit from this treatment and went on to have Botox ($n = 1$) and ileal conduit surgery ($n = 1$). This figure is similar to what Morales et al. [18] found in their study – 71% of their patients showed partial or complete response after 12 weeks of treatment. In their study, however, there was moderate decrease in effectiveness beyond 24 weeks. Kallestrup et al. [17] demonstrated a positive response in 55% ($n = 11$) of their patients over a 3-years follow-up period. There

was moderate decrease in frequency, nocturia and pain scores (5.2-fold decrease in 3 years).

There is very little in the literature on the use of intravesical HA for the treatment of recurrent UTIs. Current treatment options include the use of prophylactic antibiotics, estrogen replacement therapy in post-menopausal women, drinking cranberry juice and life-style modifications, which involves increased fluid intake, regular bladder emptying especially after sex. None of these options has been shown to have long lasting results and the search for alternatives has intensified. It is postulated that a deficiency of glycosaminoglycan in the bladder epithelium is a factor in the etiology of PBS, recurrent UTIs and bladder carcinoma [9–13]. Constantinides et al. [13] piloted the use of intravesical HA for the treatment of recurrent UTIs in 2004. Forty women received intravesical HA once weekly for 4 weeks and then once monthly for 4 months. There was no recurrence during the 5-month treatment phase and 70% of patients were recurrence-free at 1 year follow-up. The median time to recurrence was about 3 months (pre-treatment) and 17 months (post-treatment). The treatment was well tolerated by the patients. Lipovac et al. [21] instilled intravesical HA in 20 women with recurrent UTIs over 6 months and demonstrated a reduction in the number of infections per person per year from 4.99 ± 0.92 to 0.56 ± 0.82 ($p > 0.001$). The mean time to recurrence increased from 76.7 ± 24.6 to 178.3 ± 25.5 days ($p > 0.001$). About 65% of the patients were recurrence-free at 48 weeks. More recently, in a randomized, double-blinded, placebo-controlled study, Damiano et al. [22, 23] showed 77% decrease in infection rate per person per year following intravesical instillation of HA and chondroitin sulphate to patients with recurrent UTI. Additionally, the average time to recurrence improved from 52.7 ± 33.4 to 185.2 ± 78.7 days compared to placebos.

We recruited 13 patients with documented recurrent UTIs who were on long-term prophylactic antibiotics into this study. On average, each patient received 9 instillations of intravesical HA over 23 weeks. At 21-month follow-up, 53% ($n = 7$) of our patients had shown complete response and had come off their antibiotics. Amongst the non-responders 3 patients (50%) continued to be on rotating low dose prophylactic antibiotics. Two patients with DOA and recurrent UTIs have had ileal conduits formed and one patient is currently being counseled for an ileal conduit.

The results from our study along with those from Constantinides et al. [13], Lipovac et al. [21], Damiano et al. [22, 23] do lend credence to the theory of glycosamino-

glycan deficiency in the bladder epithelium of patients with recurrent UTIs. Our patients tolerated intravesical HA well and we recommend considering this viable option in patients with recurrent UTI and PBS/IC early to help symptoms, reduce pain and improve QoL.

Conclusion

Intravesical sodium hyaluronate (Cystistat[®]) can be used with minimal side effects and good compliance in both groups of patients with PBS and recurrent UTIs. Our data suggests patients with PBS have a better response to intravesical sodium hyaluronate (Cystistat[®]) in comparison to patients with recurrent UTIs. Longer follow-up and larger patient numbers in both groups will be required to confirm the long-term efficacy of these 2 clinically challenging entities.

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