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ORIGINAL ARTICLE

Hyaluronan treatment of interstitial cystitis/painful bladder syndrome

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Abstract The aim of this study is to evaluate the efficacy of intravesical hyaluronan therapy in interstitial cystitis/painful bladder syndrome (IC/PBS). One hundred twenty-six patients with IC/PBS and an average disease duration of 6.1 years were treated with weekly instillations of a 50-cm^3 phosphate-buffered saline solution containing 40 mg sodium hyaluronate. To be eligible for hyaluronan treatment, a positive modified potassium test was requested as a sign of a urine–tissue barrier disorder. Data were obtained by a visual analogue scale (VAS) questionnaire rating from 0 to 10 that asked for global bladder symptoms before and after therapy. Additional questions evaluated the therapeutic impact on quality of life. A positive and durable impact of hyaluronan therapy on IC/PBS symptoms was observed—103 (85%) of the patients reported symptom improvement (≥2 VAS units). The mean initial VAS score of 8.5 decreased to 3.5 after therapy ($p<0.0001$). Out of 121 patients, 67 (55%) remained with no or minimal bladder symptoms after therapy (VAS 0–2). The majority (101, 84%) reported significant improvement of their quality of life. Intravesical therapy had to be initiated again with good success in 43 patients (34.5%) as symptoms recurred after discontinuation of treatment, while the rest stayed free of symptoms for up to 5 years. In general, hyaluronan therapy was well tolerated and, with the exception of mild irritative symptoms, no adverse reactions were reported for a total of 1,521 instillations. Timely hyaluronan instillation therapy may lead to complete symptom remission or even cure in part of the IC/PBS patients, while some responders need continuous intravesical therapy. The present results suggest that selection of patients for hyaluronan therapy by potassium testing improves the outcome of intravesical therapy with a response rate of >80%.

Keywords Interstitial cystitis · Hyaluronan · Instillation therapy · GAG substitution · Hyaluronic acid

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Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic inflammatory disease of the bladder wall that is characterised by bladder pain and a variety of voiding symptoms [1]. The multifactorial aetiology and obscure pathogenesis as well as too rigid and restrictive diagnostic criteria in the past are responsible for the fact that controlled studies on IC/PBS therapies are rare and mostly include only small numbers of patients that are heterogeneous as to their symptoms and duration of disease. Thus, present therapeutic recommendations are mainly based on empiric data [2].

One of the favourite pathophysiologic hypotheses for IC/PBS proposed throughout the last decades is based on a disorder of the urine–tissue barrier [3, 4]—disturbance of the balance between hyperosmolaric urine and the physiologic tissue compartment and penetration of toxic urinary compounds into the bladder wall ("urothelial hyperpermeability"), as also seen in acute cystitis, induce urgency, frequency and pain. As an essential contributor to the protective barrier at the urothelial level, glycosaminoglycans (GAGs) have played an important role in pathophys-

iologic, diagnostic and therapeutic IC/PBS concepts. GAGs are long, linear polysaccharide compounds synthesized by urothelial cells and associated to the urothelial cell membrane, where they reinforce the surface and form an additional permeability barrier by water binding and consecutive volume increase. GAGs play a major role in urothelial homeostasis by reduction of the direct contact of urine with the urothelium [5, 6]. GAG deficiency has been suggested as a primary cause not only of IC/PBS but also of ulcerative colitis and Crohn's disease [7].

Although reports about the demonstrability of GAG deficiency as well as the proposed urothelial hyperpermeability in IC/PBS patients have been controversial, GAG substitution concepts have obtained a predominant position in IC/PBS therapy with appreciable response rates [8–13]. In a recent survey among European IC/PBS experts, GAG substitution was rated as first-line therapy (personal communication, third meeting of the European Society for Studies in Interstitial Cystitis, Baden, Austria, June 16–18, 2005).

At present, three GAG substituents (heparin, hyaluronan—the correct term for the therapeutic drug derived from hyaluronic acid which is too acidic for intravesical use—and chondroitin sulphate) and one heparinoid (pentosan polysulphate (PPS)) are available for substitution therapy. For oral PPS, efficacy has been proven despite conflicting results [10]. Reports on the therapeutic use of chondroitin sulphate are sparse [12, 13].

For intravesical hyaluronan therapy, several uncontrolled studies have shown excellent efficacy in IC/PBS with response rates up to 70% [9, 14, 15], as well as in other chronic inflammatory bladder diseases such as radiation and recurrent bacterial cystitis [16, 17]. However, these studies include only small numbers of patients and, with one exception, the follow-up is less than 1 year. Encouraged by the promising results of intravesical hyaluronan therapy, we offered this therapy as a first-line treatment to our IC/PBS patients and evaluated the outcome by means of a standardised questionnaire.

Materials and methods

Since year 2000, 121 female patients with confirmed diagnosis of IC/PBS and an average disease duration of 6.1 years (0.5–12) were treated at two institutions with weekly instillations of a 50-cm^3 phosphate-buffered saline solution containing 40 mg sodium hyaluronate (Cystistat®, Bioniche Pharma Group, Inverin, Co. Galway, Ireland). To be eligible for hyaluronan treatment, a positive modified potassium test was requested, i.e. patients had to show a >30% reduction (difference) of maximal bladder capacity (test) with consecutive instillation of saline and 0.2 M KCl (as described by Daha et al. [18]) prior to initiation of hyaluronan therapy.

Instillation therapy was only performed in patients who were able to retain the instillations for a minimum of 2 h. All patients were instructed to take 50 mg nitrofurantoin on instillation days to prevent urinary tract infection from catheterism. All instillations were performed with hydrophilic 10 F Foley catheters. Instillations were continued until patients were either free of IC/PBS symptoms or until symptoms had significantly improved to their satisfaction and no more instillations were requested. Instillations were discontinued in the absence of any beneficial effect reported by patients after a maximum of ten instillations.

Data were obtained by means of a questionnaire which was mailed to the patients at a mean 6.5 months after their last hyaluronan instillation. The questionnaire asked for assessment of global-bladder- or IC-related symptoms at the time of the last instillation and at the time of completion of the questionnaire, using a visual analogue scale (VAS) rating from 0 to 10 (0 = no symptoms; 10 = maximal symptoms), as compared to pretreatment symptoms that were recorded before initiation of therapy. Additional questions evaluated the overall impact of instillation therapy on quality of life and if patients would decide to undergo instillation therapy again.

In a statistical analysis of data, mean VAS symptom scores were determined for the pretreatment and posttreatment as well as follow-up periods, and values were compared using the Wilcoxon signed-rank test.

Results

The mean age of the 121 IC/PBS patients was 49.4 years (17–83 years). The mean maximal bladder capacity with the modified potassium test was 322.5 cm^3 (28–700) with saline and 190.8 cm^3 (5–450) with 0.2 M KCl. The mean difference was 41%. The time of completion of the study questionnaire was an average of 6.5 months after the last instillation. The average number of instillations for all patients was 12.2 (SD±7.4; Table 1).

A positive and durable impact of hyaluronan therapy on IC/PBS symptoms was apparent in the assessment of pretreatment and posttreatment VAS scores (Table 2)—initial VAS symptom scores were high with a mean score of 8.5 (4–10), which means that most patients had severe, close to maximal bladder symptoms. Following hyaluronan instillation therapy, 85% of the patients reported symptom improvement ≥2 VAS units, and the observed decrease of the mean VAS score to 3.5 (0–10) was significant ($p<$ 0.0001). At the time of questionnaire completion, the VAS score improvement remained stable at 3.5 (0–10). The mean decrease of VAS scores from pretreatment to post-instillation was −5.0 (−59%). Nineteen patients reported a VAS score of 0 at the end of instillation therapy, and a total

Table 1 Hyaluronan instillation history and patient impact

Parameter	Hyaluronan-treated patients (n=121)
Follow-up time after last instillation (months)	
Mean	6.5
Minimum–maximum	0.0–23.0
Total number of instillations	
Mean±SD	12.2±7.4
Minimum–maximum	1.0–40.0
Reinstitution of hyaluronan therapy to maintain therapeutic effect—42 (34.5%)	
Patient impact	
Did therapy improve QoL?	
Yes	101 (84%)
No	20 (16%)
Would agree to instillation therapy in the future?	
Yes	103 (85%)
No	18 (15%)

SD Standard deviation, *QoL* quality of life

of 67/121 patients (55%) remained with no or minimal bladder symptoms (VAS≤3) after therapy.

There was a high level of satisfaction with hyaluronan therapy amongst patients. The majority (84%) reported that their quality of life had improved significantly with intravesical therapy and a similar number (86%) would agree to repeat hyaluronan instillations in the future if necessary.

Although the initial hyaluronan instillation regimen was continued until IC/PBS symptoms had either disappeared or were significantly improved, intravesical therapy had to be initiated again in 34.5% of the patients as symptoms recurred after discontinuation of treatment (Table 1). By this regimen, the beneficial therapeutic effect was maintained.

In general, hyaluronan therapy was well tolerated and, with the exception of mild irritative symptoms consequent to catheterisation and cystitis episodes when anti-infective prophylaxis was not performed, no adverse reactions were reported over the whole treatment period and a total of 1,521 instillations.

Discussion

The response rate of 85% in the present series is remarkably higher than those reported by Morales et al. (71%) [9] and Kallestrup et al. (65%) [15] and may be a consequence of treatment procedures and/or patient selection. Special treatment standards were: (1) instillation times of at least 2 h, excluding all patients that were not able to retain hyaluronan long enough to exert its beneficial local effects (which also means that patients with very low functional capacities <50 cm^3 are no candidates for instillation therapy) and (2) anti-infective prophylaxis that prevents catheter-induced cystitis and, thus, symptom deterioration in a patient group prone to urinary tract infection.

Patient selection by potassium testing may be an important reason for the high response rate of the present series. The modified potassium test [18] was chosen in the present series to identify patients with a presumptive defect at the urine–tissue barrier that might be restored by GAG substitution therapy, while patients without this defect are less likely to respond to GAG substitution. This selection principle is supported by several reports demonstrating that the response to GAG substitution therapy is significantly lower in potassium-negative patients than in potassium-positive patients [19, 20], a finding that conforms to our personal experience.

Although the mean duration of IC/PBS-specific bladder symptoms was 6.1 years in the present series, the diagnosis of IC/PBS had been suggested in <20% of patients prior to presentation at our department, and no IC/PBS-specific therapy had been initiated before. Thus, patients in the present series can be regarded as IC/PBS-therapy-naïve patients, which may explain the excellent outcome that stands in contrast to the study of Whitmore et al. (personal communication and presentation, first annual meeting of the Multinational Interstitial Cystitis Association, Rome, Italy, Sept. 2004), who failed to show any difference between placebo and hyaluronan in patients who had undergone a multitude of unsuccessful therapies before and had not been subject to the selection and treatment standards of the present series as outlined before.

Most interestingly and according to the report of Kallestrup et al. [15], a part of the IC/PBS patients treated

Table 2 VAS symptom scores

Parameter	Hyaluronan-treated patients (n=121)
VAS scores (mean±SD (minimum–maximum))	
Pretreatment	8.5±1.7 (4.0–10.0)
Posttreatment	3.5±2.7 (0.0–10.0)
Follow-up[a]	3.5±2.7 (0.0–10.0)
Mean VAS score changes (mean±SD (minimum–maximum))	
Pretreatment to posttreatment	−5.0±2.8[b] (−10.0–0.0)
Posttreatment to follow-up	+0.0±2.3
Pretreatment to follow-up	−5±2.9 (−10.0–1.0)
Patient changes between pretreatment and follow-up	
Improved≥2 VAS units	103 (85%)
Improved<2 VAS units	6 (5%)
Unchanged	12 (10%)

VAS Visual analogue scale, *SD* standard deviation

[a] Follow-up assessment refers to the VAS score recorded at the time of completion of the questionnaire

[b] Pretreatment VAS score was significantly different (p<0.0001) from posttreatment and follow-up scores; scores between posttreatment and follow-up were not significantly different (p=0.7036)

with intravesical hyaluronan seems to be cured, because they do not need additional treatment after instillation therapy. In the present series, only about one third (34.5%) of the 85% of patients with symptom remission or improvement had to restart instillation therapy when symptoms recurred. This means that about 50% of the patients initially treated with intravesical hyaluronan did not need additional therapy for a follow-up of up to 5 years. Without an evidenced explanation for this phenomenon, it may be hypothesised that, in part of IC/PBS patients, timely GAG substitution may restore the urothelial or GAG defect, while in case of continuous damage to the urine–tissue barrier, GAG substitution therapy has either to be administered continuously or stays ineffective. This theory is supported by the observation that potassium-positive patients with symptom remission after GAG substitution therapy turn potassium-negative, which suggests normalisation of the urine–tissue barrier disorder, while non-responders stay potassium-positive after therapy [21, 22].

While side effects from hyaluronan as a biologic substance normally found in the bladder and other tissues are very improbable, the biochemical properties suggest superior efficacy compared to other GAG substituents. In contrast to other GAGs, hyaluronan does not appear to be integrated into cell membrane proteoglycans, but binds to a number of receptors expressed by urothelial cells (intracellular adhesion molecule (ICAM-1), receptor for hyaluronan mediated motility, cluster of differentiation 44 (CD44)), and may, thus, become part of the urine–tissue barrier when substituted by instillation [6, 23]. Other exogenous GAG species like heparin or chondroitin sulphate need to be integrated in cell membrane proteoglycans by active synthesis in an energy-consuming intracellular process (that may be impossible in damaged urothelial cells) to exert its barrier properties. The larger size of the hyaluronan molecules and the higher binding capacity of water molecules compared to other GAG substitutes suggest an improved barrier function. In addition, hyaluronan is predominantly found at the basal cell membrane, where reinforcement of the urine–tissue barrier is more consistent in contrast to superficially substituted GAGs that may be washed out with the urine. An even more important protective mechanism may be the binding of hyaluronan to cellular receptors that play a key role in inflammatory cascades (ICAM-1, CD44) [24]. This may provide an explanation for the strong anti-inflammatory effect of hyaluronan. Whether these biochemical properties or other mechanisms like the suppression of urothelial ATP-release [25] or the desactivation of the inflammation-mediating nuclear factor κB [26] or even not yet defined processes are responsible for the superior reported response rates of hyaluronan compared to other GAG substituents is still unclear.

The summary of published studies in Table 3 demonstrates the efficacy of GAG substitution therapies, suggesting that response rates for the various substituents and regimens may differ. Selection of patients for GAG substitution therapy seems crucial, and lower response rates may only be consequent to inclusion of patients without a urine–tissue barrier disorder.

The 15% non-responders to intravesical hyaluronan therapy in the present series, together with those patients who did not fulfill the enrollment criteria of a positive potassium test, stay as the challenging “core” of IC/PBS patients. It is important to find more treatment algorithms, similar to potassium testing for GAG substitution therapy, to offer and individually adapt the most promising therapies from a comprehensive repertoire and spare patients the troublesome course of therapeutic trial and error.

Being aware that the lack of control is a considerable setback in the present study but encouraged by the favourable findings in a challenging disease, a multinational controlled study on hyaluronan therapy is presently performed. The present findings give hope to IC/PBS patients that are confronted with the diagnosis of a chronic and incurable disease, because they suggest that a considerable number has a high chance of symptom improvement or even cure.

Table 3 Published studies on glycosaminoglycan substitution therapy

Author	GAG substituent	Number of patients	Study design	Response rate (%)	Time frame
Hwang, 1997 [10]	Oral pentosan polysulphate	398	Placebo-controlled (meta-analysis)	28–54	3 months
Sant, 2003 [27]	Oral pentosan polysulphate	121	Controlled (vs. hydroxyzine)	34	6 months
Bade, 1997 [28]	Intravesical pentosan polysulphate	20	Controlled (vs. placebo)	44	18 months
Steinhoff, 2002 [12]	Chondroitin sulphate	18	Uncontrolled	44.4	13 months
Parsons, 1994 [11]	Heparin	48	Uncontrolled	56	12 months
Morales, 1996 [9]	Hyaluronic acid	25	Uncontrolled	71	6 months
Kallestrup, 2005 [15]	Hyaluronic acid	20	Uncontrolled	65	3 years

Conflicts of interest None.

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