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ORIGINAL ARTICLE

Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis

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Abstract
Introduction and hypothesis While the short-term efficacy of intravesical hyaluronan for bladder pain syndrome/interstitial cystitis (BPS/IC) has been demonstrated, no data exist on the long-term outcome of this therapy.
Methods Seventy BPS/IC patients treated with intravesical hyaluronan therapy from 2001 to 2003 were asked to rate their present status of bladder symptoms on a visual analog scale.
Results Forty-eight of 70 patients responded after a mean follow-up of 4.9 years. The average initial VAS score of 8.15 had been reduced to 2.71 after therapy and further to 2.14 5 years later. Fifty percent of patients (24/48) reported complete bladder symptom remission at 5 years follow-up without any additional therapy; 41.7% (20/48) with symptom recurrence was improved with hyaluronan maintenance therapy. No improvement was reported by four patients.
Conclusions Besides a high rate of acute symptom remission, intravesical hyaluronan also shows long-term efficacy in a considerable number of BPS/IC patients.

Keywords Bladder pain syndrome · GAG substitution · Hyaluronan · Hyaluronic acid · Instillation therapy · Interstitial cystitis

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Introduction

Glycosaminoglycan (GAG) substitution therapy is one of the most popular regimens for treatment of BPS/IC. Response rates between 30% and 80% have been described with intravesical administration of various substances like hyaluronan, pentosan polysulfate (PPS), heparin; chondroitin sulfate, and DMSO. Most of these studies were uncontrolled and short-term observational. Despite acceptable response rates in these reports, no significant advantage over placebo was found when study settings were controlled [1–8].

One of the largest published series on intravesical hyaluronan therapy in BPS/IC from our institution showed >80% symptom response rate 6 months after treatment in a therapy-naïve group of patients selected by a positive modified potassium test [9]. Since long-term follow-up data for patients after instillation therapy are only addressed in a single study from Kallestrup for a small patient cohort [10], we assessed the present bladder symptom status of our patients 5 years after instillation therapy.

Materials and methods

Seventy female patients with the diagnosis of BPS/IC conforming to present ESSIC criteria ("the diagnosis of bladder pain syndrome (BPS) is made on the basis of the symptom of pain related to the urinary bladder, accompanied by at least one other urinary symptom such as daytime and night-time frequency, as well as exclusion of confusable diseases as the cause of the symptoms") who had been treated with intravesical hyaluronan 40 mg in 50 cm^3 phosphate-buffered saline (Cystistat®, Bioniche, Galway, Ireland) in the years 2001–2003, were reevaluated with a questionnaire by mail. Patients were selected for

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hyaluronan therapy by a positive modified potassium test, i.e., patients had to show a >30% reduction of maximal bladder capacity in a consecutive instillation of saline (NaCl 0.9%) and KCl 0.2 M as described by Daha et al. [11]. These patients received weekly hyaluronan instillations until symptoms resolved as to patients judgement or if instillation therapy turned out to be ineffective after a maximum of 10 instillations. Instillation therapy was only performed in patients who were able to retain the instillation for 2 h.

The questionnaire was identical to questionnaires before and after instillation therapy as published before and asked for:

1. The present status of global bladder symptoms ("Please rate the presently perceived intensity of your bladder symptoms") by a visual analog scale (VAS, 0 to 10, where 0 is no symptoms and 10 is intolerable bladder symptoms)
2. Additional therapies within the last 5 years
3. And a global judgement of instillation therapy ("Would you undergo instillation therapy again?" and "Would you recommend instillation therapy to other patients?")

Improvement was defined as a VAS score reduction of >2 points following therapy.

Statistical analysis was performed by Friedman ANOVA and Kendall Coefficient of Concordance Test ($p<0.05$) and by Randomization Test ($p<0.05$).

Results

The response rate to the questionnaire was 68.5% (48 of 70 patients). Patients' demographics are shown in Table 1. Average patients' age was 48.3 years (17–81), and the average time period after the last instillation was 4.9 years (4–6.8). The average duration of bladder symptoms in this patients group had been 6.1 years (0.5–12 years) before initiation of treatment. The average number of instillations was 11.8 (8–25).

Table 2 shows the long-term outcome of hyaluronan instillation therapy: 50% of patients (24/48) were free of bladder symptoms after hyaluronan instillation therapy for the whole observation period; their VAS was 1.4 at present follow-up. While only 8.3% (4/48) of patients did not experience any benefit from hyaluronan therapy, bladder symptoms recurred during the first year after initial improvement in 20/48 patients (41.7%). These recurrences were treated with another course of weekly hyaluronan instillations followed by monthly maintenance therapy in 12 patients, supported by a daily dose of oral pentosanpolysulfate in another eight patients. The VAS at present follow-up for this group with maintenance treatment was 2.4. The four nonresponders were also treated with a combination of intravesical hyaluronan and oral PPS to maximize GAG substitution therapy, and later with alternative therapies like amitryptilin, however, without success.

VAS scores before therapy and throughout follow-up are shown in Tables 3 and 4 as well as Fig. 1. The average initial VAS score for all patients was 8.15 (SD± 1.67), decreased to 2.71 (SD±1.96) immediately after hyaluronan therapy, stayed stable at 6 months post instillation therapy with an average 2.7 (SD±2.1), and showed a further reduction to 2.14 (SD±2.31) 5 years later. VAS score reduction after therapy was statistically significant ($p=0.0001$).

A VAS score reduction of >2 was observed in 85.4% of patients (41/48), whereas 6.25% (3/48) showed a reduction <2%, and 8.3% (4/48) reported no improvement. While initial VAS scores were similar for three treatment groups (group 1: single course of intravesical hyaluronan with permanent remission, group 2: repeat course and maintenance of hyaluronan therapy, group 3: maintenance with intravesical hyaluronan and oral PPS), group 1 had the lowest VAS score after 5 years of follow-up (1.4) vs. 2.4 in group 2 and 4.1 in group 3 that included the four nonresponders.

No statistical correlation was found between patient age or duration of BPS/IC symptoms and the grade of symptom remission.

Discussion

The efficacy of hyaluronan is based on several mechanisms that aim on the urothelial function disorder present in BPS/IC: on one side, hyaluronan reinforces the urine-tissue barrier by integration in the GAG layer on the luminal surface and the base of urothelial cells; on the other side, unique antiinflammatory mechanisms have been identified, like inhibition of leukocyte migration, adherence of immune complexes, and

Table 1 Hyaluronan instillation history

Mean age	48.3 years (17–81)
Mean follow up time	4.9 years (4–6.8)
Mean disease duration before hyaluronan therapy	6.1 years (0.5–12)
Total numbers of hyaluronan instillations mean	11.8 (8–25)
Questionnaire response rate	68.5% (48/70)

Table 2 Long-term follow-up after initial hyaluronan instillation therapy

Stable symptom improvement after primary therapy *without* any further therapy during follow up	50% (24/48 pat.)
Stable symptom improvement *with* intermittent hyaluronan instillation therapy during follow up	25% (12/48 pat.)
Stable symptom improvement *with* intermittent hyaluronan instillation therapy *and* oral PPS during follow up	16.7% (8/48 pat.)

binding to specific receptors (I-CAM 1, CD 44) involved in the inflammatory process [12–14].

The present report is the first that assesses treatment results 5 years after hyaluronan instillation therapy. Even with the setback of an uncontrolled study and a nonresponse rate to the questionnaire of 31.5% which reduces the response rate in an intention-to-treat analysis to 34%, there are several important conclusions that can be drawn from the data:

1. Intravesical hyaluronan therapy may lead to persistent symptom remission in a selected group of BPS/IC patients. In conventional terms, these patients, 50% in the present survey, may be regarded as cured from their disease. However, late recurrences surpassing the observation period cannot be excluded.
2. Part of the patients with symptom remission after intravesical hyaluronan therapy relapses early within the first year; however, treatment response was maintained by continuation of instillation therapy throughout the whole observation period. In some patients, oral PPS was added to the GAG substitution regimen, if either they were not able to regularly come to instillations for an extended period of time or if hyaluronan therapy alone did not improve symptoms to patients expectations. (n=12)
3. Hyaluronan long-term therapy has no adverse effects and can be administered over years without disadvantage for the patients.

The only comparable long-term results were reported by Kallestrup [10]: in this series, 20 BPS/IC patients had been treated with intravesical hyaluronan for 3 months (four weekly and two monthly instillations) and were followed for 3 years. After the initial 3 months of treatment, 65% of patients reported symptom improvement (nocturia was reduced 40%, pain 30%) and continued monthly hyaluronan instillations up to 3 years. About 50% of these patients stopped therapy within this 3 years period because of complete symptom remission, while the other 50% still kept monthly maintenance therapy and were judged as partial responders. These data are confirmed by the present report.

Similar results as in the present study have not been reported for other GAG substituents. Response rates after initial instillation therapy were 45% for chondroitin sulfate, 56% for heparin, and 44% for PPS [5–7]. Long-term results do not exist for these substances.

The high response rate in the present study may be a consequence of patient selection and standardization of instillation therapy:

1. The modified potassium test is believed to indicate a disorder at the urine-tissue barrier. Only patients with a positive test were included in the present study. This set of patient responds better to GAG substitution therapy, whereas potassium negative patients show a very low response rate of about 20% [15–17]. Only recently, it was shown that successful hyaluronan instillation therapy with symptom remission reverses positive potassium sensitivity to normal [18].
2. Patients were treatment-naive for BPS/IC, i.e. hyaluronan therapy was their first disease-specific therapy. Patients

Table 3 VAS symptom scores throughout the observation period

VAS Scores (mean ± SD (minimum–maximum))	
Pretreatment	8.15 ± 1.7 (4.0–10.0)
After instillation therapy	2.71 ± 1.96 (0.0–8.0)
6 months after therapy	2.70 ± 2.1 (0.0–8.0)
5 years after therapy	2.14 ± 2.31 (0.0–8.0)
VAS reduction 5 years after initial hyaluronan therapy	
Improvement >2 VAS units	41 (85.4%)
Improvement <2 VAS units	3 (6.25%)
Unchanged	4 (8.35%)
Absolute VAS values at 5 years follow-up	
VAS 0 (asymptomatic)	16 (33.3%)
VAS 1–2 (mild symptoms, no subjective need for therapy)	14 (29.2%)
VAS >2 (moderate symptoms, request for therapy)	18 (37.5%)

Table 4 VAS scores in responders, maintenance therapy and non-responder groups

	Group 1 (CR after HA)	Group 2 (HA maintenance)	Group 3 (PPS+HA maintenance) responders	non-responders
No. patients (total 48)	24	12	12	
Responders/Nonresponders	24/0	12/0	8	4
Initial VAS	8.9	9.0	8.0	8.0
VAS after therapy	2.9	2.5	2.5	8.0
Present VAS	1.4	2.4	4.1	8.0

CR complete remission, *Ha* hyualuronian, PPS pentosan polysulfate

with a number of unsuccessful preceding treatments represent a negative selection of possibly advanced or neuropathic disease, which usually does not respond to GAG substitution therapy.

3. The average number of instillations was almost 12 in the present series and, thus, appreciably higher than in the reports of other investigators that normally used a schedule of four weekly followed by two to four monthly instillations.
4. To be eligible for the protocol, patients had to be able to retain the hyaluronan instillation for at least 2 h. Shorter bladder contact times show less efficacy. Thus, patients with low bladder capacities (and possibly more advanced disease) were not included. Anti-infective prophylaxis with nitrofurantoin 50 mg on instillation days prevented bladder infections from catheterism, which counteract the beneficial effect of intravesical hyaluronan.
5. The 8.3% of patients that did not respond to hyaluronan instillation therapy stayed unimproved after 5 years, i.e. also other therapies that were initiated during this period did not influence symptomatology. This subset of BPS/IC patients stays the "hard core" that needs to be subject of future investigations.

In summary, besides a high rate of acute symptom remission, intravesical hyaluronan also showed long-term efficacy in a considerable number of BPS/IC patients in the present study, which suggests that some patients may be cured by this therapy. Patients with symptom recurrence after instillation therapy have a high chance for symptom remission with hyaluronan maintenance therapy.

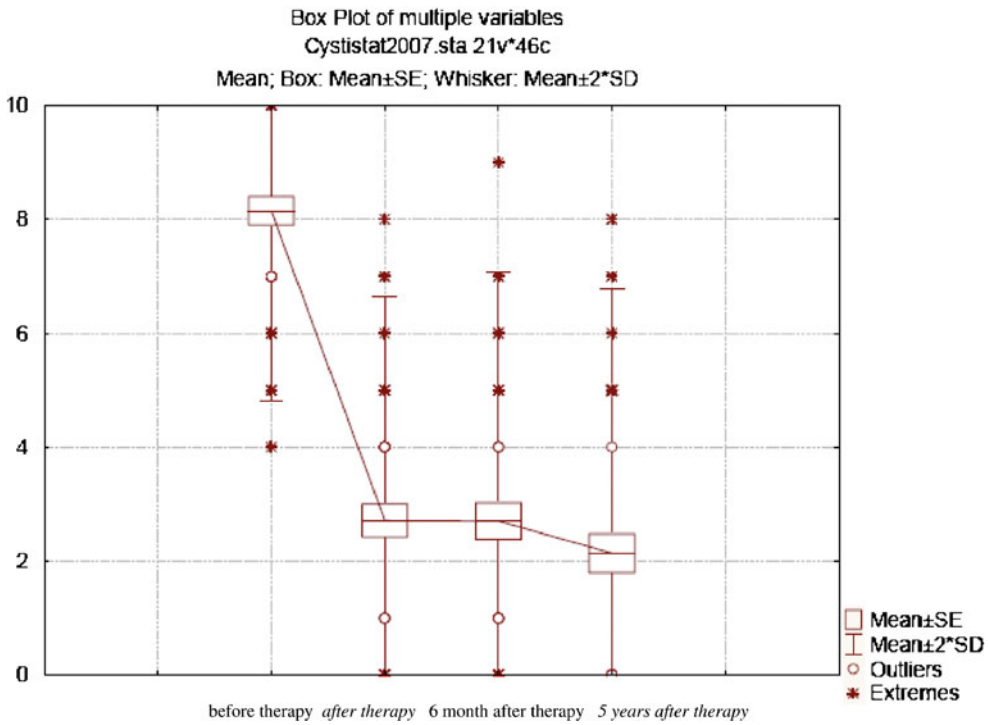

Fig. 1 Box plot figure of VAS symptom score during follow-up

Conflicts of interest Claus R. Riedl is the principal investigator for controlled study on Hyaluronan in BPS/IC (CISTIC).

References

1. Toft BR, Nordling J (2006) Recent developments of intravesical therapy of painful bladder syndrome/interstitial cystitis: a review. Curr Opin Urol 16:268–272
2. Morales A, Emerson L, Nickel JC, Lundie M (1996) Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol 156:45–48
3. Fall M, Oberpenning F, Peeker R (2008) Treatment of bladder pain syndrome/interstitial cystitis 2008: can we make evidence-based decisions? Eur Urol 54:65–78
4. Porru D, Campus G, Tudino D, Valdes E, Vespa A, Scarpa RM, Usai E (1997) Results of treatment of refractory interstitial cystitis with intravesical hyaluronic acid. Urol Int 59:26–29
5. Bade JJ, Laseur M, Nieuwenburg A, van der Weele LT, Mensink HJ (1997) A placebo controlled study of intravesical pentosanpolysulfate for the treatment of interstitial cystitis. Br J Urol 79:168–171
6. Parsons CL, Housley T, Schmidt JD, Lebow D (1994) Treatment of interstitial cystitis with intravesical heparin. Br J Urol 73:504–507
7. Steinhoff G, Ittah B, Rowan S (2002) The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 9:1454–1458
8. Nickel JC, Egerdie B, Downey J, Singh R, Skehan A, Carr L, Irvine-Bird K (2009) A real-life multicentre clinical practice study to evaluate the efficacy and safety of intravesical chondroitin sulphate for the treatment of interstitial cystitis. BJU Int 103(1):56–60
9. Riedl CR, Engelhardt PF, Daha KL, Morakis N, Pflüger H (2008) Hyaluronan treatment of interstitial cystitis/painful bladder syndrome. Int Urogyneocol J Pelvic Floor Dysfunct 19(5):717–721
10. Kallestrup EB, Steinunn S, Jørgense S, Nordling J, Hald T (2005) Treatment of interstitial cystitis with Cystistat®: a hyaluronic acid product. Scand J Urol Nephrol 39:143–147
11. Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pfluger H (2003) Comparative assessment of maximal bladder capacity, 0.9% NaCL versus 0.2M KCl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol 170:807–809
12. Hurst RE (1994) Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. World J Urol 12:3–10
13. Leppilahti M, Hellström P, Tammela TLJ (2002) Effect of diagnostic hydrodistension and four intravesical Hyaluronan Instillations on bladder ICAM-1 intensity and association of ICAM-1 intensity with clinical response in patients with interstitial cystitis. Urology 60:46–51
14. Schulz A, Vestweber AM, Dressler D (2009) Anti-inflammatory action of a hyaluronic acid-chondroitin sulphate preparation in an in vitro bladder model. Akt Urol 40(2):109–112
15. Parsons CL, Forrest J, CJ CJ, the Elmiron Study Group (2002) Effect of pentosan polysulfate therapy on intravesical potassium sensitivity. Urology 59:329–334
16. Gupta SK, Pidcock L, Parr NJ (2005) The potassium sensitivity test: a predictor of treatment response in interstitial cystitis. BJU Int 96:1063–1066
17. Teichman JM, Nielsen-Omeis BJ (1999) Potassium leak test predicts outcome in interstitial cystitis. J Urol 161:1791–1796
18. Daha L, Riedl CR, Lazar D, Simak R, Pflüger H (2008) Effect of intravesical glycosaminoglycan substitution therapy on bladder pain syndrome/interstitial cystitis, bladder capacity and potassium sensitivity. Scand J Urol 42(4):369–372