Actas Urológicas Españolas. 2011;**35(3)**:184–187

Actas Urológicas Españolas

www.elsevier.es/actasuro

CASUISTRY

Clinical and urodynamic experience with intravesical hyaluronic acid in painful bladder syndrome associated with interstitial cystitis

A.B. Figueiredo, P. Palma,* C. Riccetto, V. Herrmann, M. Dambros, R. Capmartin

Division of Female Urology, Department of Urology, Faculty of Medicine of the Campinas State University, UNICAMP, São Paolo, Brazil

Received May 20, 2010; accepted September 1, 2010

KEYWORDS
Painful bladder;
Hyaluronic acid;
Urgency;
Frequency

Abstract
Introduction: Few studies have been carried out on therapeutic options in patients with painful bladder syndrome associated with interstitial cystitis. The aim is to verify the safety and effectiveness of treatment with sodium hyaluronate through intravesical instillation in patients with painful bladder syndrome.
Materials and methods: A series of 18 female patients is presented, with a mean age of 51 years and prior diagnosis of painful bladder syndrome, who were treated by means of the weekly infusion of an intravesical solution of 40 mg of sodium hyaluronate in sterile solution, over a period of eight weeks. The patients were examined clinically and urodynamically prior to their inclusion in the study and eight months after the instillations had concluded.
Results: There was a statistically significant improvement in the urodynamic parameters and in the symptoms measured quantitatively by means of the questionnaire "Pelvic Pain and Urgency/Frequency" between the baseline situation and after the vesical instillation of sodium hyaluronate in patients with painful bladder syndrome. There was no toxicity arising from the treatment, given that no adverse effects were recorded in relation to it.
Conclusion: The clinical use of intravesical hyaluronic acid in patients with painful bladder syndrome possibly associated with interstitial cystitis has been demonstrated. The clinical improvement is also associated with an increase in the bladder's capacity and sensitivity. Tolerance was excellent. Clinical tests that more profoundly evaluate the therapeutic potential of this drug in this type of patients are required.

*Corresponding author.
E-mail: ppalma@uol.com.br (P. Palma).

0210-4806/$ - see front matter

PALABRAS CLAVE
Vejiga dolorosa;
Ácido hialurónico;
Urgencia;
Frecuencia

Experiencia clínica y urodinámica con ácido hialurónico intravesical en el síndrome de vejiga dolorosa asociado a cistitis intersticial

Resumen

Introducción: Las opciones terapéuticas en las pacientes con vejiga dolorosa asociada a cistitis intersticial están poco estudiadas. Se pretende verificar la seguridad y eficacia del tratamiento con hialuronato de sodio a través de instilación intravesical en pacientes portadoras de síndrome de vejiga dolorosa.

Material y métodos: Se presenta una serie de 18 pacientes femeninas, con edad media de 51 años y diagnóstico previo de síndrome de vejiga dolorosa, que fueron tratadas mediante la infusión de una solución intravesical semanal de 40 mg de hialuronato de sodio en solución estéril, durante 8 semanas. Las pacientes fueron evaluadas clínica y urodinámicamente antes de su inclusión en el estudio y 8 meses después de haber finalizado las instilaciones.

Resultados: Se observó una mejora estadísticamente significativa en los parámetros urodinámicos y en la sintomatología medida cuantitativamente mediante el cuestionario Pelvic Pain and Urgency/Frequency entre la situación basal y después de la instilación vesical de hialuronato de sodio en paciente con síndrome de vejiga dolorosa. La toxicidad derivada del tratamiento fue nula, puesto que no se registró efecto adverso relacionado con el tratamiento.

Conclusión: Se demuestra la utilidad clínica del ácido hialurónico intravesical en pacientes con síndrome de vejiga dolorosa posiblemente asociado a cistitis intersticial. La mejoría clínica se asocia también con aumento de la capacidad y mejora de la sensibilidad vesical. La tolerancia fue excelente. Se necesitan ensayos clínicos que evalúen en profundidad el potencial terapéutico de este fármaco en este tipo de pacientes.

Clinical problem

Systemic treatment options for patients with painful bladder syndrome associated with interstitial cystitis are limited. Interstitial cystitis is a clinical syndrome characterized by the urgency to void or frequency of urination associated with pelvic pain without a defined cause.[1]

One of the basic components of glycosaminoglycans (GAG) with specific relevance in the aetiology of interstitial cystitis is hyaluronic acid, a large mucopolysaccharide that has an important function protecting the bladder surface.[2] A deficiency in the GAG layer changes the permeability of the urothelium to urinary components, principally to potassium ions. In this sense, an excess of potassium ions in the urothelial layer may be responsible for the intense urgency and/or pain of painful bladder syndrome.[1] In individuals with a normal bladder, the epithelial layer is relatively impermeable and does not allow potassium ions to be absorbed. In the event the epithelium has a lesion, potassium ions will be absorbed, generating symptoms of pain and urgency through the stimulation of the chemical-sensitive component of type C nerve fibres.[3,4]

It has been proven that hyaluronic acid manifests an active biological variety that may help towards the improvement of patients with painful bladder syndrome associated with interstitial cystitis.[2] The main aim of our study was to verify the safety and efficacy of sodium hyaluronate through intravesical instillation in female patients diagnosed with painful bladder syndrome associated with interstitial cystitis.

Design of the study

The trial was carried out at the urology outpatients surgery of the Hospital de Clínicas da UNICAMP, in a series of 18 patients from a database of interstitial cystitis diagnoses. They were all informed on the experimental nature of the treatment and signed their consent to participate in the trial.

The patients were all treated with a weekly intravesical infusion of 40 mg of sterile sodium hyaluronate solution for a period of eight weeks. They were clinically and urodynamically evaluated prior to their inclusion in the trial, as well as eight months after the instillations were completed.

Diagnosis was based on the potassium sensitivity test (PST) and on the clinical symptoms described by the patients in accordance with the recommendations of the National Institute of Diabetes, Digestive and Kidney Diseases - 1998 on the criteria for inclusion and exclusion of the disease. The clinical trial included anamnesis with emphasis on the degree and duration of the symptoms presented, age, parity, history of gynaecological surgery, associated pathologies, medication that could affect the interstitial cystitis, hormonal condition. Physical examination included a detailed gynaecological examination to exclude other conditions. The patients answered the self-administered questionnaire on symptoms on urgency, frequency and dysuria, *"Pelvic Pain and Urgency/Frequency"* (PUF) regarding their double prevalence of symptoms and emotions, which covers the main symptoms of interstitial

Table 1 Administration protocol of endovesical hyaluronic acid

1. Patient in lithotomy position
2. Lavage of the perineal area, vagina and urethral meatus with povidone
3. Application of 2 ml of sterile 2%lidocaine gel in urethral canal
4. Insertion of an 8 French catheter
5. Instillation of 50 ml of de Cystistat® inside the bladder
6. Removal of the catheter
7. Patient does not urinate for at least 30 minutes

cystitis, prior to treatment and 8 months subsequently. In all the cases, a double urodynamic study was carried out to assess bladder sensitivity and capacity prior and subsequent to treatment.

Results achieved

The mean age of the patients studied was 51.7 (range 20-70) years. In all the cases, the duration of the symptoms was more than 12 months. As regards the demographic and gynaecological characteristics of the patients, 78% were Caucasian, 83% multiparous, 56% menopausal and 22% used some type of hormone replacement therapy. Their average body mass index was 27 (range 18.7-37.7). All the patients presented increased urinary frequency, nocturia, micturition urgency and pain, either abdominal (45%), urethral (11%), vaginal (17%) or perineal (28%).

The principal findings of the urodynamic trial included a comparison of the first desire to void, normal desire to void, strong desire to void and bladder capacity, all prior and subsequent to treatment. We observed an increase in bladder capacity and a statistically significant improvement in bladder sensitivity ($p<0.005$) (table 1). With the PUF questionnaire, we quantified the symptoms of patients prior and subsequent to treatment and found a significant difference in all the variables related to emotion and symptom scores, and we noted a decrease by half in post-treatment values ($p<0.0001$) (table 2).

Discussion

We observed a significant change in the symptoms that accompany interstitial cystitis, prior and subsequent to

Table 2 Bladder sensitivity and capacity data

Variables	Min	Max	Mean	p-value
First Desire to Void				0.0003
Before Cystistat®	25	185	63.56	
After Cystistat®	42	235	111	
Normal Desire to Void				<0.0001
Before Cystistat®	57	240	115.61	
After Cystistat®	100	289	198.06	
Strong Desire to Void				<0.0001
Before Cystistat®	94	280	179.22	
After Cystistat®	220	410	304.33	
Maximum Cystometric Capacity				0.0002
Before Cystistat®	123	310	236.72	
After Cystistat®	297	640	403.94	

All the data is expressed in ml of 0.9%NaCl solution.

Table 3 Distribution of the PUF questionnaire score

Pelvic Pain, Urgency and Frequency (PUF)	Min	Max	Mean	p-value
Symptoms				<0.0001
Before Cystistat®	11	21	17.17	
After Cystistat®	2	12	2.40	
Emotion				<0.0001
Before Cystistat®	2	12	7.39	
After Cystistat®	0	6	2.67	
Total				<0.0001
Before Cystistat®	18	33	24.56	
After Cystistat®	6	14	10.33	

treatment with intravesical hyaluronic acid; we also noted excellent tolerance of the treatment. In a pilot trial with 25 patients, Morales et al. demonstrated a 71% improvement in the rate of symptoms after 12 weeks of endovesical instillation by means of an analogue visual scale.[5] Dahla et al. describe a symptom improvement rate of 80% in patients with a positive potassium sensitivity test after 10 weeks of intravesical application of hyaluronic acid.[4]

The clinical and urodynamic benefit that we found may be explained by the property of hyaluronic acid to inhibit the activation of mast cells and because it is one of the main substrata in the formation of the GAG chain. A reconstructed urothelium does not suffer direct aggression of potassium ions and C fibres are not activated with subsequent degranulation of mast cells.[6] The trial carried out by Nordling et al. provides a similar experience to that we describe herein, although with a three-year follow-up. It describes a long-term beneficial effect in approximately 75% of the patients and a lack of response in 20%. The majority manifested a continuous improvement in pain, in micturition frequency and in urgency.[7]

In short, we found that patients with typical symptoms and urodynamic parameters of painful bladder syndrome associated with interstitial cystitis benefited from treatment by means of the vesical instillation of sodium hyaluronate. Likewise, we found evidence that the said improvement is noticeable both in subjective parameters of the disease and in the objective parameters of urodynamics. This experience provides arguments in favour of the efficacy and safety of therapy by means of the vesical instillation of sodium hyaluronate in the treatment of interstitial cystitis and is a firm basis for the development of prospective and randomized clinical trials with patients suffering from this pathology.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Daha LK, Riedl CR, Hohlbrugger G, Knoll M, Engelhardt PF, Pflüger H. Comparative assessment of maximal bladder capa- city 0,9 NaCl versus 0,2M KCl, for the diagnosis of interstitial cystitis: a prospective controlled study. J Urol. 2003;170:807-9.
2. Morales A, Emerson L, Nickel JC. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. Urology. 1997;49(5A Suppl):111-3.
3. Parsons CL, Bullen M, Kahn BS, Stanford EJ, Willems JJ. Gynecologic presentation of Interstitial Cystitis as detected by intravesical sensibility. Obstet Gynecol. 2001;98:127-32.
4. Daha LK, Riedl CR, Lazar D, Hohlbrugger G, Pflüger H. Do cystometric findings predict results of intravesical hyaluronic acid in women with cistitis interstitial. Eur Urol. 2005;47:393-7.
5. Morales A, Emerson L, Nickel JC, Lundie M. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. J Urol. 1996;156:45-8.
6. Boucher WS, Letourneau L, Huang M, Kempuraj D, Green M, Sant GR, et al. Intravesical sodium hyaluronate inhibits the rat urinary mast cell mediator increase triggered by acute immobilization stress. J Urol. 2002;167:380-4.
7. Nordling J, Jorgensen S, Kallestrup E. Cystistat for the treatment of interstitial cystitis: a 3 years follow-up study. Urology. 2001;57(6 Suppl 1):123.