Long-term experience with sodium chondroitin sulfate in patients with painful bladder syndrome

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Objective: To assess the response of patients diagnosed with painful bladder syndrome to treatment with instillations of sodium chondroitin sulfate.

Material and methods: We present a series of cases of patients with painful bladder syndrome who followed a bladder instillation protocol with sodium chondroitin sulfate, according to our centre’s regimen. The response to treatment was assessed with respect to pain, according to the Downie scale; urinary frequency, according to the voiding diary; and subjective improvement, according to the Patient Global Impression of Improvement (PGI-I) scale.

Results: A total of 28 patients with a median age of 59 years (range 22–90) followed this protocol. From the medical histories, 19.4% had suffered an infection of the urinary tract, 3.8% had suffered urinary tuberculosis, 7.6% received pelvic radiation therapy and 26.9% had taken anticholinergic drugs for overactive bladder syndrome. We evaluated the response to treatment at 0, 3, 6 and 12 months and found that at the end of treatment 72.3% of the patients had improved bladder pain and 75% were significantly better.

Conclusions: Treatment with sodium chondroitin sulfate through endovesical instillation in painful bladder syndrome improves pain, voiding frequency and quality of life in the long term.

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**Resultados**: Veintiocho pacientes con una mediana de edad de 59 años (rango: 22-90) siguieron este protocolo. Entre los antecedentes clínicos el 19,4% había padecido alguna infección del tracto urinario, el 3,8% tuberculosis urinaria, el 7,6% recibió radioterapia pélvica y el 26,9% había tomado anticolinérgicos por vejiga hiperactiva. Evaluamos la respuesta al tratamiento a los 0-3-6 y 12 meses, encontrando que al final del tratamiento el 72,3% había mejorado del dolor vesical y el 75% de los pacientes se encontraba mucho mejor.

**Conclusiones**: El tratamiento con condroitin sulfato sódico en instilación endovesical en el síndrome de vejiga dolorosa produce mejora del dolor, de la frecuencia miccional y de la calidad de vida a largo plazo.

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**Introduction**

Chronic inflammatory bladder disease has been observed in the context of many diseases, among which stand out interstitial cystitis, urinary tuberculosis, radiation-induced cystitis, overactive bladder, recurrent bladder infections and many more diseases. As several authors have attempted to demonstrate in interstitial cystitis, chronic damage of the bladder wall may cause impairment in the mucin glycosaminoglycan (GAGs) layer and may become permeable to urinary solutes.

The hallmark symptoms of chronic inflammatory bladder disease typically include urinary frequency, urgency, and pain on bladder. Several treatments have been used in its management: oral and intravesical therapy and in the complex cases surgery was used. The GAG deficit hypotheses on the etiology of painful bladder syndrome have led to development of many intravesical preparations containing GAG. The goals are repair bladder wall, relieve symptoms and improve quality of life of patients.

There are various commercially available GAG preparations. Chondroitin sulfate is the only one which has shown differences versus placebo in a randomized double-blind study. Based on these assumptions, our goal has been to confirm the long-term efficacy (12 months) of intravesical chondroitin sulfate solution (Uracyst®) in the treatment of various forms of chronic cystitis.

**Patients and methods**

A series of cases of patients with painful bladder syndrome is presented, all with pain of bladder origin and increased urinary frequency, treated with intravesical chondroitin sulfate 2% (Uracyst®) therapy from January 2011 to May 2012. Prior to voiding, 20ml of the solution was instilled. Treatment schedule was one instillation a week for 4 consecutive weeks, followed by once-monthly for one year. Patients had to retain the instillation for at least 30 min.

The diagnosis of painful bladder syndrome was carried out according to a detailed history, a thorough physical examination and endoscopic findings which ruled out bladder cancer and other specific bladder conditions. All patients underwent urine culture testing, cystoscopy and cytology before undergoing instillation therapy.

Subjective improvement was assessed for each patient by numerical pain rates scale of Downie, detailed voiding diaries (daytime and nighttime voiding frequency) and Patient Global Impression Improvement (PGI-I) scale. Variables were analyzed before treatment and at 3, 6 and 12 months after treatment.

To determine correlation between pain and urinary frequency (daytime and nighttime) with the presence of cervical trigonitis and recurrent UTI, statistical analysis was performed using the Mann–Whitney U test.

**Results**

Twenty-eight patients (27 women, 1 man) with pain of bladder origin and increased urinary frequency followed the therapy protocol. Average patients' age was 59 years (22–90). Two patients were excluded from the study because they could not be evaluated for long-term monitoring.

Five patients (19.4%) had a history of recurrent urinary tract infections; one patient (3.8%) had bladder tuberculosis; two (7.6%) had been treated with pelvic radiotherapy and seven patients with patients overactive bladder (26.9%) had been treated with anticholinergics.

There were no significant side effects. Only one patient reported voiding pain after first instillation, and her response to anti-inflammatory therapy did not require treatment discontinuation.

Endoscopic findings revealed grossly normal bladder mucosa in 18 patients (69.2%), areas of cervical trigonitis in 5 (19.4%), hemorrhagic cystitis in 2 patients (7.6%) and in 1 patient (3.8%) tuberculosis cystopathy. At the moment of the study cytologies and urine cultures were negative. Bladder biopsy was performed in 3 patients (11.5%) showing chronic cystitis in two patients and interstitial cystitis in the third. Two episodes of urinary tract infection by *Escherichia coli* were reported during treatment, but not related to intravesical instillations. Mean follow-up was 9 months.

Before treatment, bladder pain showed a median of 7 (range from 3 to 10; average 6.5). Patients reporting complete disappearance of pain within 3, 6, and 12 months after treatment were 58.3%, 66.7% and 72.2%, respectively. After 3, 6 and 12 months of initiation of treatment, the median pain score decreased to 1.67, to 1.46 and to 0.83, respectively (Fig. 1).

Regarding urinary frequency, daytime median frequency was 10 (3–16) and nighttime median frequency was 5 (0–10) before treatment. These values are not associated with cervical trigonitis or a history of repeated urinary infection ($p > 0.05$). At 3 months, daytime voiding frequency is reduced to 6 (3–16) times, and nighttime frequency to 2
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Figure 1 Pain improvement (A) and urinary frequency (B) after 3–6–12 months.

(0–10). At 6 months, daytime median frequency remains in 6 (3–16), and nighttime median frequency in 1 (0–8). At 12 months, daytime and nighttime medians frequencies were 5 (4–15) and 2 (0–6), respectively (Fig. 1).

No association between pain and cervical trigonitis or recurrent urinary tract infection (p > 0.05) was detected. According to the PGI-I scale 60% of patients reported improvement in their condition at 3 months, the rate increased slightly at 6 months reaching 64%. The improvement was more evident at 12 months, feeling much better in 75% of patients (Fig. 2). In any case, there was no worsening of symptoms after treatment.

Discussion

Chondroitin sulfate efficacy is based on several mechanisms, although there is consensus in stating that it repairs the defect in the GAG layer of the bladder.1,13 The most accepted hypothesis to explain this layer impairment is that the epithelium may become permeable to urinary solutes, resulting in immunity-inflammation activation and subsequent chronic pain.5 Diseases such as interstitial cystitis, overactive bladder, recurrent bladder infections or pelvic radiotherapy may cause chronic bladder damage with loss of the protective barrier.

The first studies on the treatment of interstitial cystitis assessed the efficacy of intravesical administration of substances such as lidocaine, corticosteroids, and heparin. Relief of interstitial cystitis symptomatology was observed, but the follow-up was short and the number of patients small.10,11 Studies on intravesical instillation of dimethyl sulfoxide (DMSO) or pentosan polysulfate sodium (PPS) showed very mixed results and after therapy discontinuation, most patients relapsed.8,9 Hyaluronic acid is another substance most commonly used in the treatment of interstitial cystitis. Nordling et al. proved first its long-term effectiveness (3 years) improving symptoms in patients with interstitial cystitis.14 Later, they analyzed

Figure 2 Global improvement after 3 months (A) (n = 5), 6 months (B) (n = 25) and 12 months (C) (n = 20).
the value of hyaluronic acid in the prevention of recurrent bladder infections.\textsuperscript{13} In the same way, Mañas et al. used hyaluronic acid successfully to control the number of episodes of urinary tract infection in patients with spinal cord compression.\textsuperscript{16} Recent trials and van Hooven have shown the efficacy of chondroitin sulfate intravesical versus placebo in relieving symptoms for at least 12 months.\textsuperscript{1-3} Although the efficacy of oral therapy has been demonstrated in several studies, especially in combination, the results obtained do not show statistically significant differences and side effects have been reported.\textsuperscript{8}

Present study shows a significant improvement of pain relief and urinary frequency in the first 3 months of treatment. After one year, the rate increased by about 15% in patients who completed the protocol. Curtis et al. in a randomized study compared treatments of intravesical chondroitin sulfate versus placebo, and obtained similar results; however the difference was not statistically significant and the follow-up was only 12 weeks.\textsuperscript{1} Using protocol for bladder instillation of chondroitin sulfate similar to our trial, Sorensen demonstrated symptomatic improvement in 73.1% of patients diagnosed with interstitial cystitis; optimal response was achieved between 4 and 6 months of treatment.\textsuperscript{11} Once again, Nordling and van Ophoven in a multicenter study with chondroitin sulfate to treat various types of chronic cystitis, obtained positive results; the follow-up duration was short.\textsuperscript{17} Patients undergoing pelvic radiation therapy for cancer and treated with intravesical instillation of chondroitin sulfate and hyaluronic acid had also showed a tendency to symptomatic improvement.\textsuperscript{14,18} All these studies show that chondroitin sulfate intravesical instillation is a first-line treatment alternative for painful bladder syndrome/chronic cystic disease associated with multiple diseases.

It would be desirable to know whether the results are durable one year after treatment. Further studies (longer-term randomized controlled studies) are needed to confirm patient recovery or, on the contrary, the patients could benefit from some type of intravesical maintenance therapy longer.

Conflict of interest

The authors declare that they have no conflict of interest.

References