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Experiencia con glucosaminoglicanos intravesicales para el tratamiento de patologías crónicas del tracto urinario inferior

Intravesical Glycosaminoglycans Experience for Chronic Lower Urinary Tract Pathology Treatment

Verónica Tobar Roa[2] Juliana Alvarez Jaramillo[1]

[1] Centro Urológico FOSCAL, UNAB Urology Postgraduate Teacher, Bucaramanga, Santander, Colombia
[2] Universidad Autónoma de Bucaramanga (UNAB), Bucaramanga, Santander, Colombia

Address for correspondence Verónica Tobar Roa, Centro Urólogico FOSCALCra 24 # 154 - 106, Tower B 10th Floor Module 62, Floridablanca, Santander, Colombia (e-mail: vergot19@hotmail.com).

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Abstract

Objective Intravesical glycosaminoglycans (GAG) treatment is one of the therapeutic options for chronic bladder pathologies and is approved for Bladder Pain Syndrome (BPS), radiation cystitis, and recurrent urinary tract infections (UTIs). The purpose of this study is to describe the demographic characteristics of patients with such pathologies in our population and to evaluate treatment response.

Methods It is a retrospective study of patients with the aforementioned pathologies, who received treatment with GAG. Demographic characteristics and subjective improvement with treatment were evaluated. A bivariate analysis was performed to study possible improvement predictors.

Results 53 patients were evaluated. Of them, 33 (62.3%) with BPS, 12 (22.6%) with recurrent UTIs, and 8 (15.1%) with radiation cystitis. The dose range received was between 4 - 20 instillations, with a median of 6 doses. 67.9% of patients showed improvement of symptoms with treatment, this percentage being even higher for the group of patients with recurrent UTIs (91%). No treatment response predictors were found.

Conclusions Intravesical GAG treatment is a therapeutic alternative for patients with chronic bladder pathologies, with satisfactory results in the medium term. Prospective studies are needed to support the findings of this study.

Keywords
- chronic pain
- urinary tract infection
- interstitial cystitis
- glycosaminoglycans
- hyaluronic acid

Resumen

Objetivo El tratamiento con glucosaminoglicanos intravesicales hace parte de las opciones terapéuticas de las patologías crónicas de la vejiga y se encuentra aprobado para el tratamiento de síndrome de vejiga dolorosa (SVD), cistitis por radiación e infección urinaria recurrente. El objetivo de este estudio es describir las características demográficas de los pacientes con dichas patologías en nuestra población y evaluar la respuesta al tratamiento.

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Métodos Estudio retrospectivo de pacientes con las patologías mencionadas, quienes recibieron tratamiento con glucosaminoglicanos. Se evaluaron las características demográficas y la respuesta al tratamiento. Se realizó un análisis bivariado para estudiar posibles variables predictoras de mejoría.

Resultados Se evaluaron 53 pacientes. De estos, 33 (62.3%) con síndrome de vejiga dolorosa, 12 (22.6%) con infección urinaria recurrente y 8 (15.1%) con cistitis por radiación. El rango de dosis recibida estuvo entre 4-20 instilaciones, con una mediana de 6 dosis. El 67.9% de los pacientes tuvo una respuesta adecuada al tratamiento, siendo este porcentaje aún mayor para el grupo de pacientes con IVU recurrente (91%). No se encontraron factores predictores de respuesta al tratamiento.

Conclusiones El tratamiento con GAG intravesicales es una alternativa terapéutica para pacientes con patologías crónicas de la vejiga, con resultados satisfactorios a mediano plazo. Se necesitan estudios prospectivos que soporten los hallazgos de este trabajo.

Palabras clave
- dolor crónico
- infección de vías urinarias
- cistitis intersticial
- glucosaminoglicanos
- acido hialurónico

Introduction

Glycosaminoglycans (GAG) correspond to the mucopolysaccharides family that form the main structure of the extracellular matrix, along with other molecules such as collagen, elastin, fibronectin, and laminin.[1] In the bladder, the most frequent GAG are hyaluronate, heparin and heparan sulfate, dermatan sulfate, chondroitin sulfate, and keratan sulfate.[1,2] This GAG layer covers the urothelium, providing a protective barrier against microorganisms, ions, carcinogens, and other irritating agents, guaranteeing the integrity and protection at the level of the bladder mucosa. The lack of these substances has been related to chronic lower urinary tract pathologies such as Bladder pain syndrome (BPS), recurrent urinary tract infection (recurrent UTIs) and radiation cystitis.[2–4] Therefore, the repair of the mucosa through the intravesical application of GAG has been proposed among the therapeutic options for these pathologies.[5]

The purpose of this study is to describe the demographic characteristics of patients with BPS, radiation cystitis, and recurrent UTI in our population, as well as to evaluate the response to intravesical GAG treatment in these three clinical conditions.

Methods

A retrospective cohort study was conducted between January 2015 and April 2019, including men and women over 18 years of age, with the previously described lower urinary tract pathologies, which received treatment at Centro Urológico FOSCAL, with intravesical instillations of GAG (chondroitin sulfate plus sodium hyaluronate 1 g-800mg / 50ml or sodium hyaluronate 40mg / 50ml) in a minimum of 4 doses.

Of the total of 57 patients, 4 were excluded due to lack of data or minimal follow-up, thus leaving 53 patients for analysis.

The demographic characteristics of the patients, parity, pelvic oncological and surgical history, previous treatments, and number of doses received were obtained from an anonymized database.

A visual analogue scale (VAS) of improvement was applied to each patient 3 months after the last intravesical instillation on a scale of 0–100%, considering a clinically significant improvement of symptoms 50% or more.

The study was performed under the institution's ethics and research committee guidelines. Statistical analysis was performed in STATA VE 12 software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). A univariate and bivariate analysis was performed to study possible variables associated with a better response to treatment.

Results

The mean age was 61 years, and the majority of patients were women. ►**Table 1** shows the demographic characteristics of the group, and ►**Fig. 1**, the distribution according to the diagnosis.

17% of the patients had a history of previous oncological pathology involving the pelvic organs and 68% had received previous radiotherapy and / or pelvic surgery. Only 9.5% suffered from a diagnosed psychiatric illness.

The vast majority of patients had received multiple treatments before GAG's instillation [►**Table 2**]. Patients concomitantly receiving analgesics or other pain modulators were not excluded. No patient was receiving antibiotic prophylaxis during the GAG's treatment period.

The range of doses received was between 4 - 20 instillations, with a median of 6 doses, administered as follows: initial cycle with a weekly dose for 4 weeks and maintenance cycle with a monthly dose, after the initial cycle.

36 patients (67.9%) presented an improvement in symptoms of at least 50% in the VAS; this percentage is even higher for the group of patients with recurrent UTI's (91%), followed by radiation cystitis (62%) and finally BPS (60%), with an overall improvement of 67.9% at an average follow-up of 2 years [►**Figure 2**].

Table 1 Patient characteristics

Parameters	n= 53
Age (years, mean)	61.5 (±11.33)
Sex	
Female	47 (88.7%)
Male	6 (11.3%)
Parity	
Yes	21 (44.7%)
No	26 (55.3%)
G0	26 (55.3%)
G1	4 (8.5%)
G2	2 (4.3%)
G3 or more	15 (31.9%)
Previous pelvic Oncological pathology	
Cervical cancer	5 (9.4%)
Rectal cancer	2 (3.8%)
Prostate cancer	1 (1.9%)
Endometrial cancer	1 (1.9%)
Previous Pelvic Radiotherapy	9 (17%)
Previous Pelvic Surgery	27 (50.9%)
Psychiatric Disease	
Anxiety Disorder	2 (3.8%)
Depressive Disorder	3 (5.7%)

Regarding the bivariate analysis, no predictive factors of treatment response with statistical significance were found within this study [►**Table 3**].

Discussion

Our study demonstrates the usefulness of intravesical GAG's treatment in BPS, recurrent UTIs, and radiation cystitis.

Table 2 Treatments

Parameter	n= 53
Previous treatment received	52 (98.1%)
Anticholinergics	33 (62.3%)
Antibiotics	28 (52.8%)
Tricyclic antidepressants	19 (35.8%)
Gabapentin / pregabalin	11 (20.8%)
Intravesical therapy	9 (17%)
- Heparin plus corticosteroid plus local anesthetic	7
- Dimethylsulfoxide (DMSO)	2
PFMT	2 (3.8%)
Botulinum toxin	2 (3.8%)
Intravesical therapy with GAG's	
Number of doses (average)	6.68 (±3.49)
Percentage improvement	49.81% (±31.77)
Follow-up in months	27.5 (±2.17)

*Guias del ICS 2019 Standards.
PFMT, Pelvic Floor Muscle Therapies.

Exogenous GAG therapy has been used for the treatment of chronic inflammatory bladder diseases for several years.[3,6,7] Even though it has been a widespread therapy worldwide, the available experience with the use of GAG is scarce, with few randomized clinical trials. Furthermore, studies focused primarily on BPS, while studies for recurrent UTIs and radiation cystitis are found in a smaller proportion.[3]

In BPS, some studies show significant improvement with treatment, although with a short follow-up (3–10 months).[2,8] Riedl et alt showed significant improvement in the VAS of 55% of the symptoms in BPS after treatment with intravesical GAG, in the same way in which Engelhart et al reported a decrease in symptoms from 81% to 27% in the immediate post-treatment., 27% at 6 months and 24% at 5 years after therapy.[8,9] These

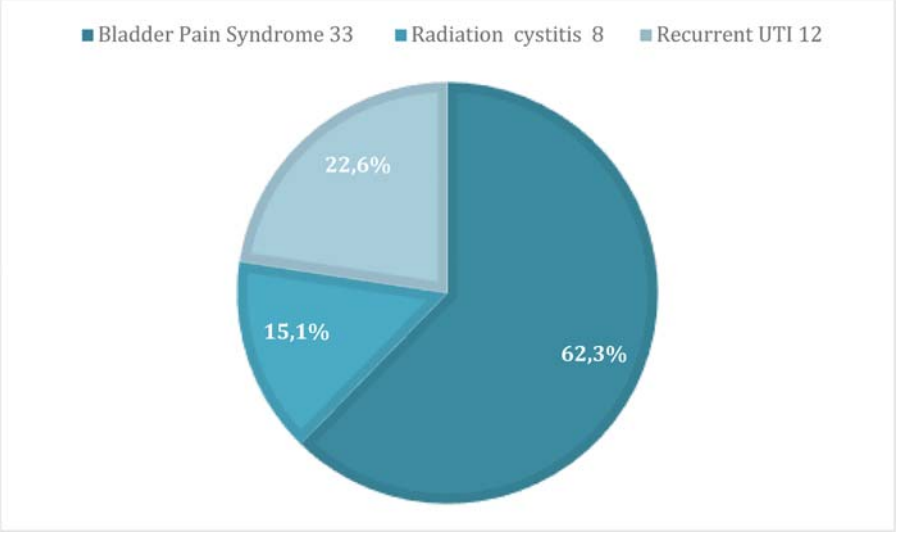

Fig. 1 Distribution according to diagnosis.

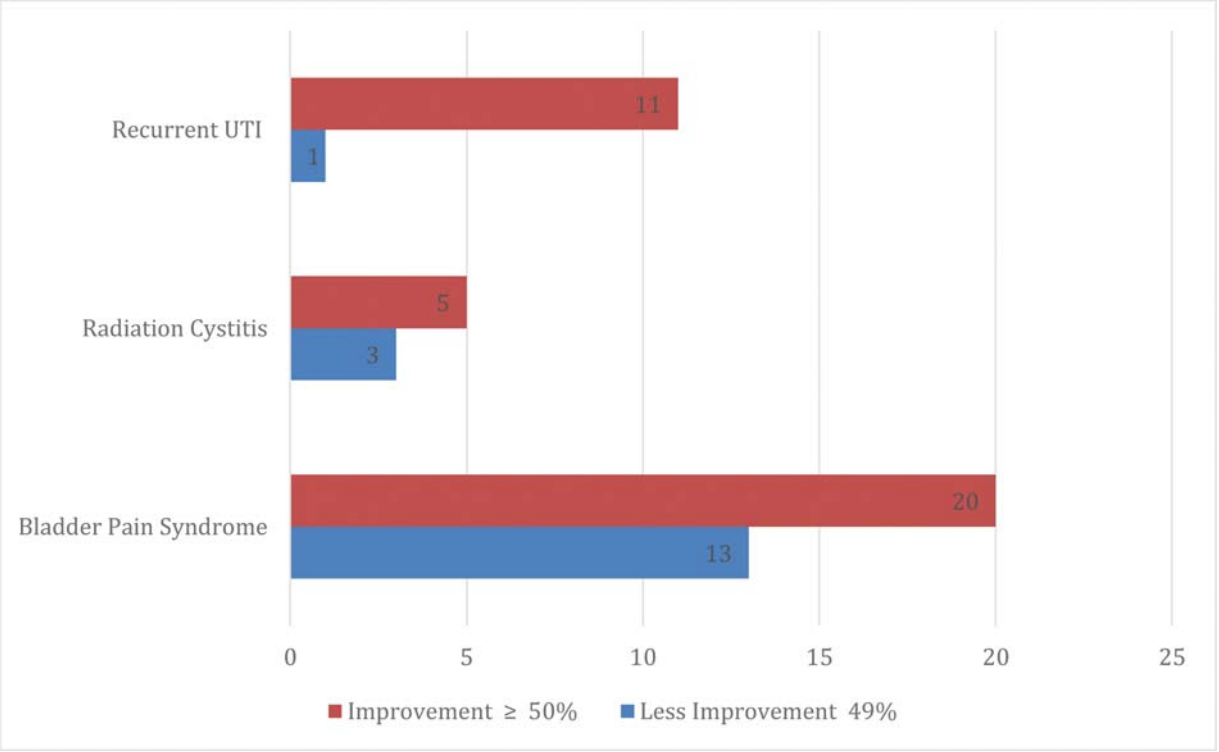

Fig. 2 Improvement greater than or equal to 50% with intravesical GAG's according to the diagnosis.

Table 3 Factors associated with significant improvement

Factors associated with improvement > 50%	RR (IC95%)	p
Age	0.99 (0.98–1.01)	0.80
Sex	0.46 (0.14 - 1.44)	0.18
Parity	0.97 (0.68–1.39)	0.90
Pelvic oncological pathology	0.82 (0.57–1.17)	0.28
Pelvic radiation therapy	0.97 (0.59–1.61)	0.93
Pelvic surgery	0.86 (0.59–1.24)	0.43

findings are similar to what we found in our study, demonstrating more than 50% improvement in symptoms in 60% of patients with BPS. Cervigni et al reported improvement in bladder diaries and VAS of frequency, urgency, and dysuria.[10]

On the other hand, Akbay et al demonstrated that intravesical therapy with GAG's was more effective in patients older than 51 years,[11] which differs with the findings of our study, where we did not find age as a predictor of treatment response. In this same study, the number of pregnancies did not prove to be a predictive factor for improvement in VAS,[11] as in our research.

There are few studies reported in the literature with the use of GAG for recurrent UTIs and radiation cystitis. Lipovac et al in their study of 2006 in women with recurrent UTIs, reported a recurrence time after the first instillation of 178 days, compared with 77 days before treatment.[4] Likewise, the most recent meta-analysis has shown a positive effect, reducing the number of UTI episodes to 2.6 per patient/year, prolonging the recurrence time of each UTI episode to 130 days.[12] Constantinides et al demonstrated that the use of GAG decreased the number of UTI's patient/year from 4.3 episodes to 0.3 and that 70% were free of recurrence at 12 months follow-up.[13] According to the findings of our study, 91% of patients with recurrent UTIs reported improvement > 50% of symptoms with the use of intravesical GAG, as has been shown by other authors.

Similarly, the use of intravesical GAG's could be effective in reducing symptoms in post-radiation patients.[14] Gacci et al in their study in patients with prostate cancer managed with radiotherapy, reported a significant reduction of urinary symptoms after 12 weeks of intravesical therapy with GAG.[14] Samper et al evaluated patients with cervical or endometrial cancer treated with brachytherapy, showing that those treated with GAGs had lower bladder toxicity.[15] This was also demonstrated in our research, with 62% improvement in patients who received intravesical GAG for symptoms related to radiation therapy.

In our study, the population that benefited most from the use of intravesical GAG the group of patients with recurrent UTIs (91%), followed by radiation cystitis (62%) and finally BPS (60%), unlike what has been documented in the literature, where the main studies performed have been directed to the treatment of BPS.

It is worth mentioning that our study has limitations, mainly due to its retrospective nature. In addition to the above, in the group of UTIs, the reduction in the number of episodes of infection and the time elapsed between episodes of cystitis was not objectively evaluated; only the subjective improvement reported by the patients was analyzed. It is also important to mention that we used the diagnostic

criteria for BPS proposed by ICS (recurrent or persistent chronic pelvic pain, pressure or discomfort perceived to be related to the bladder accompanied by at least one other urinary symptom such as urgency or frequency, in the absence of any identifiable pathology which could explain these symptoms), but additional studies such as cystoscopy or bladder biopsy were not taken into account, nor were the groups divided into the various chronic pelvic pain subtypes.

Despite these limitations, we consider that the research findings are very useful in clinical practice, since it was possible to demonstrate the effectiveness in a group of chronic pathologies where the therapeutic options are scarce.

Conclusions

Intravesical GAG treatment is a therapeutic alternative for chronic bladder diseases, with satisfactory results in the medium term. Prospective studies are needed to support the findings of this work.

Conflict of Interests
The authors have no conflict of interests to declare.

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