

Original Article

Int Neurourol J 2015;19:85-89

<http://dx.doi.org/10.5213/inj.2015.19.2.85>

pISSN 2093-4777 · eISSN 2093-6931

Intravesical Sodium Chondroitin Sulphate to Treat Overactive Bladder: Preliminary Result

Lokman Irkilata¹, Mustafa Aydın¹, Hasan Riza Aydın¹, Hüseyin Cihan Demirel¹, Mustafa Kadihasanoglu², Mustafa Kemal Atilla¹

¹Department of Urology, Samsun Training and Research Hospital, Samsun, Turkey

²Department of Urology, Istanbul Training and Research Hospital, Istanbul, Turkey



Purpose: This study aimed to verify the efficacy and safety of intravesical treatment with sodium chondroitin sulfate (CS) in patients with overactive bladder (OAB) who are refractory to previous antimuscarinic treatment.

Methods: This study was performed between June 2012 and January 2015 and included 31 consecutive women (mean age, 42.10 ± 7.34 years) with OAB who had been previously treated with two types of antimuscarinic drugs. The results of gynecologic and cystoscopic examinations were normal, and OAB comorbidity was absent. Treatment with intravesical instillations containing 40 mL CS (0.2%; 2 mg/mL) was administered for 6 weeks; after weekly treatments, monthly treatments were administered. The OAB-validated 8 (OAB-V8) symptom scores, nocturia, frequency, urgency, urge incontinence, and urinary volumes measured by uroflowmetry were evaluated for all the patients. The values obtained before the treatment were statistically compared with those obtained six months after the treatment.

Results: The duration of the symptoms was 18.36 ± 6.19 months. A statistically significant improvement of the patients' conditions was observed in terms of the OAB-V8 symptom scores, nocturia, frequency, urgency, urge incontinence, and urinary volumes measured by uroflowmetry after the treatment.

Conclusions: Despite the limitations of this study, the outcomes confirmed that CS therapy is safe and effective for the treatment of OAB.


Keywords: Chondroitin Sulfates; Administration Intravesical; Urinary Bladder, Overactive

• **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Overactive bladder (OAB) syndrome is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1]. The incidence of OAB is 12%-17%, and the prevalence is 53.1% [2-5]. It is estimated that 50-100 million people have OAB [6]. Idi-

opathic detrusor overactivity is the common cause of OAB. However, detrusor overactivity is a urodynamic finding, while OAB is a symptomatic diagnosis [7]. Detrusor overactivity can be neurogenic or myogenic whereas OAB is idiopathic. Chronic OAB symptoms significantly affect patient's quality of life, but its objective clinical and histologic findings have not been determined [8-11]. In addition, the similarity in symptoms between OAB and interstitial cystitis further makes a definitive

Corresponding author: Lokman Irkilata  <http://orcid.org/0000-0002-0141-8199>
Department of Urology, Samsun Training and Research Hospital, Fevzi Çakmak Mahallesi, Altun Yunus Soakak, Liva Park Sitesi, B-2 Blok İlkadım, Samsun, Turkey
E-mail: irkilatamd@gmail.com / Tel: +90-533-715-3627 / Fax: +90-362-277-8569
Submitted: March 13, 2015 / **Accepted after revision:** May 11, 2015



This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

diagnosis difficult. First-line pharmacological treatment comprises antimuscarinic agents, the use of which may be limited owing to their tolerability, efficacy, and long-term compliance [7]. Advances in elucidating the pathophysiology of OAB and alternative targets for pharmacological therapy have led to the development of newer agents to manage this condition. One such agent is sodium chondroitin sulfate (CS), a natural polymer of a disaccharide composed of a chain of glucuronic acid and N-acetyl glucosamine sulfated either in the 4 or 6 position and is present naturally in the human body [12]. Glucosamine sulfate is the main component of the glycosaminoglycan layer, which protects urinary epithelium from toxic substances [13]. This study evaluated, retrospectively, the efficacy of intravesical 80 mg/40 mL sodium CS (0.2%) (neutral-PH, containing no preservatives or adjuvants) in patients with OAB who had no improvement in their symptoms even after the use of several antimuscarinics.

MATERIALS AND METHODS

This study originally included 33 consecutive patients who had normal gynecological functions, normal cystoscopic findings, and no disease underlying their OAB between June 2012 and January 2015. Patients with following conditions were excluded: who had stress or mixed incontinence with more than 100 mL residual urine, those with prolapse, underlying neurological disease, and intolerance to the first administration of intravesical treatment. Two patients could not tolerate the treatment and left the study; the study finally had 31 patients.

For diagnosis before treatment and follow-up after treatment, patients filled out the validated Turkish version of the OAB-validated 8 (OAB-V8) questionnaire (Table 1) [14,15]. The OAB-V8 comprises the first 8 questions of the OAB questionnaire (OAB-q) and has been translated into many languages. The OAB-q is recommended for use in screening and monitoring OAB [14-16].

Study participants had OAB with unresolved symptoms in spite of treatment with antimuscarinic agents (at least two active agents for at least 3 months but which had been discontinued for at least 1 month). Efficacy of intravesical sodium CS sulfate treatment was retrospectively evaluated in the patient group administered intravesical sodium CS.

Our treatment protocol included one application of 80 mg/40 mL sodium CS (0.2%) weekly for 6 weeks. One month after the last administration, patients were followed up. Before monthly treatment, patients were evaluated using OAB-V8 form for nocturia, frequency, and urgency, and uroflowmetry (UFM) also performed to determine the efficacy of treatment and whether or not the treatment had to be continued. OAB-V8 scores, nocturia, frequency, urgency, urge incontinence, and urine volumes in UFM before treatment were compared to those recorded 6 months after treatment.

IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis. The Shapiro-Wilk test was used to assess normality of data. Results of descriptive analyses are given as mean ± standard deviation, number (%), and median (range). Statistical analyses for the patient group were performed using paired samples t-test and Wilcoxon paired sam-

Table 1. OAB-V8 questionnaire

To what extent do the following cause discomfort?	Not at all	A little bit	Somewhat	Quite a bit	A great deal	A very great deal
Frequent urination during the daytime hours?	0	1	2	3	4	5
An uncomfortable urge to urinate?	0	1	2	3	4	5
A sudden urge to urinate with little or no warning?	0	1	2	3	4	5
Accidental loss of small amounts of urine?	0	1	2	3	4	5
Night-time urination?	0	1	2	3	4	5
Waking up at night because you have to urinate?	0	1	2	3	4	5
An uncontrollable urge to urinate?	0	1	2	3	4	5
Urine loss associated with a strong desire to urinate?	0	1	2	3	4	5
Total score						
OAB score ^{a)}						

OAB, overactive bladder; OAB-V8, OAB-validated 8.

^{a)}If your gender is male, add 2 points to the total score.

Table 2. Comparison of the study parameters before and after treatment (n = 31)

Parameter	Pretreatment	Posttreatment	P-value
Nocturia, median (range)	4 (2–7)	1 (0–2)	< 0.001
frequency, median (range)	8 (7–10)	5 (5–7)	< 0.001
Urine volume (mL), mean \pm SD	306.26 \pm 56.11	388.00 \pm 39.12	< 0.001
Urge incontinence, n (%)	21/31 (67.7)	2/31 (6.5)	< 0.001
OAB symptom score, mean \pm SD	20.55 \pm 4.77	8.42 \pm 1.96	< 0.001

SD, standard deviation; OAB, overactive bladder.

ples test. P-values less than 0.05 were considered statistically significant.

RESULTS

All 33 patients were female with a mean age of 42.10 ± 7.34 years. Two patients were excluded owing to intolerance to the intravesical treatment; the study finally comprised 31 patients. Mean symptom duration was 18.36 ± 6.19 months. Duration of antimuscarinic agents use in these patients was found to be 11.67 ± 4.40 months (range 2–20 months). The antimuscarinic agents used were, in order of frequency, fesoterodine, solifenacin, propiverine hydrochloride, and trospium chloride. While urgency fully resolved in 29 patients (93.5%), 2 patients did not show complete improvement but revealed some decrease in complaints. Table 2 showed nocturia, frequency, urine volume in UFM, urge incontinence, OAB symptom scores, before and after treatment. All parameters showed some improvement after treatment ($P < 0.001$).

Although complete symptomatic relief of urgency or incontinence was not reported in two patients, some improvement in both symptoms was reported. Moreover, at the end of the 6th month, all 31 patients were satisfied with the outcome of therapy and stated that they wanted to continue treatment.

DISCUSSION

OAB is a widespread troublesome disorder known to have considerable impact on quality of life and to be underdiagnosed and undertreated by physicians. The pathophysiology of OAB has not been fully explained. Generally, it is thought that non-preventable detrusor contractions play a role. The two classic theories about this condition are the myogenic theory and the neurogenic theory [11,17]. According to the neurogenic theory, changes in the central peripheral and local innervation of the

bladder result in detrusor overactivity. The study by Chancellor and de Groat [11] focused on local innervations and showed that one of the causes of OAB may be the reflex to urinate as a result of over stimulation of unmyelinated C-afferent fibers. Therefore, the idea that intravesical treatment approaches may be effective against OAB is obvious, as in our study. The theories related to OAB pathophysiology form the basis of OAB treatment approaches. Patients who do not benefit from first-line treatments for OAB, such as behavioral therapies, are recommended to choose second-line treatments such as antimuscarinic agents and β -3 adrenoceptor agonists such as mirabegron [18]. Currently, antimuscarinic agents are the most commonly used first-choice drugs for the treatment of OAB, although they have been associated with troublesome side effects and may lack efficacy. In addition, compliance and persistence with treatment remains a problem with antimuscarinic agents [7]. In situations where second-line treatments are refractory or are not tolerated, third-line treatments are recommended [18]. Third-line treatments include onabotulinum toxin A therapy, peripheral tibial nerve stimulation, and neuromodulation. In addition to the invasive nature and infection risks of third-line treatments, the greatest disadvantages are increased postvoid residuals and lack of rapid recovery [18]. Intravesical chondroitin treatment does not carry the risks of third-line treatments for patients not responding to antimuscarinic agents. However, the need to administer the treatment over several months in the hospital environment may be a disadvantage.

The differential diagnosis between OAB and interstitial cystitis further complicates the treatment of OAB. Interstitial cystitis is a debilitating, chronic disease characterized by urinary urgency, frequency, and bladder and pelvic pain, which have a profoundly negative effect on quality of life [19]. Despite worldwide scientific studies and research, there remains little consensus on the etiology and effective treatment of interstitial cystitis. Hence, diagnosis is dependant on inclusive and exclusive clini-

cal diagnostic criteria based on guidelines of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [20]. When viewed from this aspect, interstitial cystitis remains a diagnosis of exclusion, with no cystoscopic or pathologic findings that can be used for a definitive diagnosis.

It has been suggested that strict application of NIDDK criteria would have resulted in misdiagnoses in more than 60% of patients who were regarded by researchers as definitely or likely to have interstitial cystitis [10]. This means that patients who present with urgency, frequency, and nocturia potentially could be diagnosed with either OAB or interstitial cystitis. Therefore, it is not easy to differentiate OAB from interstitial cystitis, and different treatment modalities can be used without a differential diagnosis. Gauruder-Burmester et al. [21] determined that instillation of sodium CS for treatment of interstitial cystitis also is effective in treating overactive bladder based on the assumption that the glycosaminoglycan layer may be damaged in overactive bladder as well. They found that restoring the glycosaminoglycan layer with intravesical sodium CS improved symptoms in patients with OAB. In addition, they demonstrated that the symptom improvement observed after treatment with 0.2% sodium CS persists even after 24 months [22].

In spite of positive results obtained by Gauruder-Burmester et al. [21,22], CS is still not widely used for treatment of persistent OAB.

Sodium CS treatment for overactive bladder is not sufficiently well reported. We employed intravesical sodium CS therapy for OAB treatment. However, as explained above, for refractory OAB patients, intravesical sodium CS treatment is a promising alternative to overcome the disadvantages of third-line treatment since it is reversible and has no serious complications; hence, it should be considered before using third-line treatment. Patients in this study were diagnosed with OAB, had undergone treatment with different therapeutics, some of which they could not recall, and had been treated with at least two types of antimuscarinics. Patients with OAB are often administered antibiotics without appropriate indications. Patients refractory to antimuscarinics were treated with intravesical sodium CS. OAB symptom scores were 20.55 ± 4.77 before treatment and decreased to 8.42 ± 1.96 after treatment. Patients stated that their symptoms improved significantly. They reported subjectively that nocturia symptoms were no more bothersome and their sleep quality improved. Although some patients had been reluctant to participate in the study owing to invasive nature of therapy, all patients who completed the study were satisfied with the outcome and decided

to continue therapy. Owing to the development of the glycosaminoglycan layer, instillation treatment with 0.2% sodium CS resulted in a sustained improvement or treatment of OAB symptoms [21,22].

Although intravesical sodium CS treatment for OAB had positive outcome, the fact that this study was not prospective or randomized presents major limitations. In addition, using OAB-q instead of OAB-V8 to evaluate treatment results in patients would have shown not only resolution of symptoms but also improvement in quality of life, making the results more valuable.

In conclusion, intravesical sodium CS treatment may be an effective and reliable alternative to third-line treatment for patients with OAB refractory to antimuscarinic agents or not well tolerated. In spite of the limitations stated above, results of this study are encouraging. However, additional randomized clinical trials are required to confirm these findings.

ACKNOWLEDGEMENTS

We gratefully acknowledge expert statistician Naci Murat for re-evaluating our study data.

REFERENCES

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21:167-78.
2. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001;87:760-6.
3. Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20:327-36.
4. Yamanishi T, Chapple CR, Chess-Williams R. Which muscarinic receptor is important in the bladder? *World J Urol* 2001;19:299-306.
5. Lapitan MC, Chye PL; Asia-Pacific Continence Advisory Board. The epidemiology of overactive bladder among females in Asia: a questionnaire survey. *Int Urogynecol J Pelvic Floor Dysfunct* 2001;12:226-31.
6. Miller JJ, Sand PK. Diagnosis and treatment of overactive bladder. *Minerva Ginecol* 2005;57:501-20.

7. Jayarajan J, Radomski SB. Pharmacotherapy of overactive bladder in adults: a review of efficacy, tolerability, and quality of life. *Res Rep Urol* 2013;6:1-16.
8. Gimbel H, Zobbe V, Andersen BJ, Sorensen HC, Toftager-Larsen K, Sidenius K, et al. Lower urinary tract symptoms after total and subtotal hysterectomy: results of a randomized controlled trial. *Int Urogynecol J Pelvic Floor Dysfunct* 2005;16:257-62.
9. Curhan GC, Speizer FE, Hunter DJ, Curhan SG, Stampfer MJ. Epidemiology of interstitial cystitis: a population based study. *J Urol* 1999;161:549-52.
10. Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol* 1999;161:553-7.
11. Chancellor MB, de Groat WC. Intravesical capsaicin and resiniferatoxin therapy: spicing up the ways to treat the overactive bladder. *J Urol* 1999;162:3-11.
12. Baeurle SA, Kiselev MG, Makarova ES, Nogovitsin EA. Effect of the counterion behavior on the frictional-compressive properties of chondroitin sulfate solutions. *Polymer* 2009; 50:1805-13.
13. Hurst RE. Structure, function, and pathology of proteoglycans and glycosaminoglycans in the urinary tract. *World J Urol* 1994;12:3-10.
14. Acquadro C, Kopp Z, Coyne KS, Corcos J, Tubaro A, Choo MS, et al. Translating overactive bladder questionnaires in 14 languages. *Urology* 2006;67:536-40.
15. Tarcan T, Mangir N, Ozgur MO, Akbal C. OAB-V8 overactive bladder questionnaire validation study. *Urology Bull* 2012;21:113-6.
16. Oh SJ, Son H, Kim SW, Lee KS, Choo MS, Kim SO, et al. Psychometric properties of the Korean version of the overactive bladder questionnaire (OAB-q) in a Korean population. *Int Neurourol J* 2012;16:77-85.
17. Mostwin JL. Pathophysiology: the varieties of bladder overactivity. *Urology* 2002;60(5 Suppl 1):22-6.
18. Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Cullkin DJ, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol* 2012;188(6 Suppl):2455-63.
19. Brinkmann OA, Hertle L. The pathogenesis of interstitial cystitis-many hypotheses, but etiology remains uncertain. *Urologe A* 2000;39:520-6.
20. Wilkins EG, Payne SR, Peard PJ, Moss ST, Maskell RM. Interstitial cystitis and the urethral syndrome: a possible answer. *Br J Urol* 1989;64:39-44.
21. Gauruder-Burmester A, Wildt B, Tunn R. Treatment of overactive bladder with sodium chondroitin sulphate. *Zentralbl Gynakol* 2006;128:336-40.
22. Gauruder-Burmester A, Popken G. Follow-up at 24 months after treatment of overactive bladder with 0.2% sodium chondroitin sulphate. *Aktuelle Urol* 2009;40:355-9.