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Original Article

Safety and efficacy of Intravesical hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome

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ABSTRACT

Objective: To evaluate the safety and efficacy of intravesical instillation of hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome.

Material and methods: Forty patients were subjected to intravesical instillations of hyaluronic acid/chondroitin sulfate weekly for 4 weeks and at 6., 8., 12. and 16. weeks, afterwards. Then we evaluated the efficacy of this treatment modality by determining the mean changes in visual analogue scale (VAS) pain score, the pelvic pain and urgency/frequency questionnaire, the O'Leary-Sant interstitial cystitis symptoms index/problems index and 3 day-voiding diary results including daily number of voids and mean voided volume at 2 weeks, 3, and 9 months after the last dose (4th month) and urodynamic studies including cystometric capacity, 1st sensation of urination, and Q-max at 9 months after the last dose.

Results: Thirty-seven patients (6 males 16.2%, 31 females 83.8%) completed the entire follow-up protocol of this study. Age of the patients ranged from 22 to 37 years (mean, 30.7±4.18 years) and their body mass indexes (BMIs) ranged between 29 and 37 kg/m^2 (mean, 33.5±2.58 kg/m^2). An initial response to treatment in all parameters at variable degrees was noticed at 2 weeks after the last instillation when compared to the baseline, and these changes were statistically significant ($p<0.001$). Progressive improvement in all test parameters was noticed at 3 months after treatment, and this improvement was statistically significant compared with baseline and 2 weeks after treatment, respectively ($p<0.001$).

Conclusion: Intravesical instillation with both hyaluronic acid/chondroitin sulfate in the treatment of refractory painful bladder syndrome is safe, effective and well tolerated by all patients with no recorded side effects.

Keywords: Chondroitin sulfate; hyaluronic acid; painful bladder.

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Introduction

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic clinical syndrome characterized by a bladder/pelvic pain and urinary dysfunction, such as increased frequency and urgency, with a strongly negative impact on patients' quality of life.[1,2] According to the European Society for the Study of Interstitial Cystitis, BPS should be diagnosed when chronic (>6 months) pelvic pain or pressure found to be related to the urinary bladder, associated with at least one other urinary manifestation like urgency or frequency. Also, confusable diseases as the cause of the symptoms must be excluded.[3]

The etiology of IC/BPS is still not well understood, and different hypotheses have been formulated, including autoimmune processes, allergic reactions, chronic bacterial infections, exposure to toxins or dietary elements, and psychosomatic factors.[4,5] It has been hypothesized that IC/BPS could be pathophysio-

logically related to a disruption of the bladder mucosa with consequent loss of glycosaminoglycans (GAGs), a class of mucopolysaccharides with hydrorepellent properties, exposing the urothelium to many urinary toxic agents.[6] Once these substances penetrate into the bladder wall, a chain reaction is thought to be triggered in the submucosa, where nerve terminals produce inflammatory mediators causing mast cell degranulation and histamine secretion with consequent vasodilatation and inflammatory exudate.[7] This inflammatory response stimulates C fibers with consequent bladder pain and release of neuropeptides, producing damage to the mucosa and fibrosis of the submucosa.[8] Based on these aspects, the early repair of the bladder mucosa with intravesical application of GAGs, such as hyaluronic acid (HA) or chondroitin sulfate (CS), has been proposed as a possible treatment.[9-11]

Hyaluronic acid is a naturally occurring proteoglycan present in the GAG layer of the bladder urothelium. It has been proposed that the intravesical application of HA can promote regeneration of the GAG, the deficit of which has been demonstrated in patients with IC/BPS and is considered to play an important role in the pathogenesis of the disease. Hyaluronic acid also, has an inhibitory action on mast cells degranulation, which its activation is a crucial step in the pathogenesis of IC/BPS.[12,13] CS is another natural proteoglycan present in the GAG layer of the bladder epithelium. Like HA, intravesical instillation of CS has been used as a treatment for patients with IC/BPS, to help in the regeneration of GAG in the bladder urothelium. A previous study revealed that good control of urinary symptoms and pain was achieved with CS, suggesting that this drug may be useful in treatment of IC/BPS.[14]

In our study, we evaluated the efficacy and safety of intravesical instillation with both HA and CS in the treatment of patients with refractory bladder pain syndrome.

Material and methods

This study was a prospective study evaluating the safety and efficacy of intravesical instillation of HA/CS in the treatment of patients with refractory painful bladder syndrome and included 40 patients. All included patients were experiencing symptoms for more than 1 year. They presented to the urology department of our university hospital during the period from January 2015 to December 2017. All patients signed an informed written consent and the study was approved by the local ethics committee of Benha Faculty of Medicine. We excluded patients who had bladder cancer, bladder stones, recurrent urinary tract infection, previous history of intravesical instillation HA/CS or anticancer drugs.

Complete medical history of all patients were obtained, and they were assessed based on standard urological tests, visual analogue scale (VAS) pain scale scores, the pelvic pain and urgency/frequency (PUF) questionnaire and the O'Leary-Sant interstitial cystitis symptoms index (ICSI)/problems index (ICPI) and also 3 day-voiding diary results including daily number of voids and mean voided volume were recorded. Past, and present history of neurological disease, medical disorders of significance as diabetes mellitus, operations, trauma and any drugs used were taken into consideration. Physical examination including general, abdominal, neurological, and gynecological examinations was carried out in female patients and digital rectal examination, investigations including full routine preoperative biochemical analyses, urinalysis and culture sensitivity tests, abdominopelvic ultrasound, prostatic-specific antigen measurements for males <40 years and urodynamic studies were routinely performed.

All patients were subjected to intravesical instillation of hyaluronic acid/chondroitin sulfate as weekly instillations for 4 weeks, followed by 2 instillations every 2 weeks (at 6th and 8th week) and 2 instillations monthly (12th and 16th week) (total 8 doses). A 50 mL mixed solution of HA 1.6% and CS 2.0% was instilled through 14F urethral catheter (Laluril, IBSA Institut Biochimique SA, Lugano, Switzerland) for 60 minutes. The last dose was given at the 16th week. The first follow-up instillation was performed at 2nd week after the last dose. The second and third follow up instillations were realized at the 3rd and the 9th months after the last dose. We evaluated the efficacy of instillations by determining the mean changes in VAS scores, PUF questionnaire, the O'Leary-Sant ICSI/ICPI scores and 3 day-voiding diary results including daily number of voids and mean amount of voided urine. Urodynamic studies including cystometric capacity, 1st sensation of urination and Q-max were assessed at 9 months after the last dose.

Statistical analysis

Using Statistical Package for the Social Sciences version 16 software (SPSS Inc.; Chicago, IL, USA) the collected data were tabulated and analyzed. Categorical data were showed as numbers and percentages. Continuous data were expressed as mean ± standard deviation, and range, and tested for normality using Shapiro-Wilks test, and assuming normality at $p>0.05$. Repeated measures ANOVA was used for testing whether the means of 3 or more matched metric variables are equal. Significant repeated measures ANOVA was followed by post-hoc multiple comparisons using Bonferroni adjusted paired "t" test to detect significant pairs. $P\leq0.05$ was considered to be significant.

Results

Forty patients suffering from interstitial cystitis/painful bladder syndrome were initially included in this study, and 3 patients (1 male, 2 females) were excluded from the study as they did not complete the entire follow-up period. Thirty-seven patients (6

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Table 1. Personal characteristics of the studied group

	Value (n=37)
Age	
Mean±SD (range) years	30.7±4.18 (22-37)
Sex n (%)	
Male	6 (16.2)
Female	31 (83.8)
BMI	
Mean±SD (range)	33.5±2.58 (29-37)

BMI: body mass index; SD: standard deviation

males 16.2%, 31 females 83.8%) completed the entire follow up protocol enrolled in this study, their age ranged from 22 to 37 years with mean 30.74.18 years and BMI between 29 and 37 with mean 33.5±2.58 (Table 1).

An initial response to treatment at variable degrees in all parameters was noticed at 2 weeks after the last instillation when compared to the baseline, and these changes were statistically significant ($p<0.001$) (Table 2). Progressive improvement in all test parameters was noticed at 3 months after treatment, and this improvement was statistically significant compared with baseline and 2 weeks after treatment ($p<0.001$) (Table 2).

For a longer follow-up time and better assessment of our patient's response to treatment, the assessment of all parameters including urodynamic assessments were performed at the ninth month after the last instillation. VAS scores significantly improved when compared with baseline and 2 weeks after instillations (6.5 1.06 vs. 3.080.75, respectively), however no significant difference was noticed when compared with VAS scores at the 3rd month of the follow-up period (2.24, and 0.92 vs. 2.430.83) (Table 2).

Pain and urgency/frequency bother score, ICPI, number of voids and mean voided volumes showed significant improvement when compared with their values at baseline, however no significant difference was noted when compared with their values obtained at 2 weeks and 3 months of the follow-up period (Table 2).

Pain and urgency/frequency symptom scores, PUF total scores and ICSI values showed significant improvement when compared with those of baseline, but the improvement of these parameters at the 3rd month of the follow-up period was at greater extent when compared with those obtained at the 9th month of the follow-up period with a significant intergroup difference (Table 2).

Our patients underwent complete urodynamic assessments before instillation and at the 9th month after the last dose which demonstrated significant increase in both 1st sensation of urination, and maximum cystometric capacity values when compared with those of the baseline (81.418.5 mL, 224.744.2 mL vs. 73.2±17.9 mL, 20249.1 mL, respectively $p<0.001$). Maximum flow rates (Q-max) recorded at baseline and at the 9th month of the follow –up period did not differ significantly ($p=0.35$) (Table 2).

Discussion

The main treatment modality of the patients with IC-PBS is administration of oral and intravesical medications as recommended by both the European and American Urological Associations.[15]

In our study, we enrolled patients with symptoms refractory to other treatment modalities. All of our patients had received previous treatment protocols but they either experienced no improvement of their symptoms at all or transient improvement before they regain their previous symptoms. All patients included in our study had used protocols for life style modification and oral medical treatment as anticholinergics, analgesics and anti-inflammatory drugs. No patient received any kind of intravesical instillation of any medications. In our study, all patients underwent diagnostic cystoscopy. Hydrodistension with or without transurethral coagulation (TUC) of Hunner's lesions is one of the most commonly used and important method of treatment but its effect usually does not last for more than 3 to 6 months and about 45.8% of the patients treated by TUC of Hunner's lesions require another session for fulguration.[16] However, our treatment protocol of intravesical HA and CS instillation yielded us better results which persisted for up to 9 months after the last dose. Also, many adverse effects were reported with hydrodistension such as hematuria, bladder pain and bladder rupture which were not not encountered during our treatment.

Hyaluronic acid acts by increasing production of GAG from epithelial cells through activation of GAG enzymes that leads to increased GAG secretion, restoring normal GAG barrier production. HA also, acts by decreasing the permeability of the urothelium to urine constitutes.[17]

Many studies have been performed to assess efficacy of HA instillation and showed a wide range of symptom improvement, from 30% to 85%. Morales et al.[18] found that 71% of the patients experienced complete or partial response to HA. Their reported results differ from our results obtained by using a combination of HA and CS which resulted in complete or partial response in all patients. In 2011 Engelhardt et al.[19] reported that

about 50% of patients experienced complete symptom recurrence at the 5-year follow-up after instillation of HA alone.

Chondroitin sulfate is another natural proteoglycan which is used to replenish the protective GAG layer and its usage alone without HA yielded low response rates in comparison to our combination as reported in a multicenter study including 53 patients with Interstitial Cystitis/Bladder Pain Syndrome and after instillations of CS 2% of about 60% of the treated patients had experienced a significant improvement at 6 months In contrast, a published RCT reported that there is no advantage of CS, regarding 2.0% of the treated patients over control group after 6 weeks of treatment. In that study, many patients experienced a clinical improvement, but the difference between the two groups was not statistically significant.[20]

Although there are multiple studies and publications for assessment of the efficacy of HA and CS separately, few studies were published to assess efficacy of a combination of two GAGs including CS (2.0%) and low molecular weight HA (1.6%) which is the latest available substance for the GAG replenishment therapy.[21]

In 2008 Porru et al.[22] used 8-month-protocol with 20 instillations for treatment of 22 patients using 40 mL of 1.6% sodium HA and

Table 2. Assessment of the studied variables over the period of the study

Variable (n=37)	Baseline Mean±SD (Range)	After 2w ttt Mean±SD (Range)	After 3m ttt Mean±SD (Range)	After 9m ttt Mean±SD (Range)	Repeated measure ANOVA	p
VAS	6.5±1. 16 (4-8)	3.08±0.7* (1-4)	2.43±0.8*† (0-4)	2.24±0.9*† (0-4)	173.8	<0.001 (HS)
PUF symptom score	16.1±2.1 (13-21)	11.3±3.3* (3-16)	10.4±3.3*† (3-15)	11.9±2.6*‡ (4-15)	99.49	<0.001 (HS)
PUF bother score	8.89±1.3 (6-12)	5.88±2.3* (0-9)	5.43±2.2*† (0-8)	6.1±1.7* (1-8)	37.1	<0.001
PUF total score	25.1±3.3 (19-33)	17.2±5.5* (3-25)	15.8±5.4*† (3-23)	18.0±3.9*‡ (5-23)	70.7	<0.001
ICSI	15.5±2.2 (11-19)	11.1±2.41* (5-15)	10.2±2.3*† (5-13)	11.5±2.1*‡ (7-15)	213.7	<0.001
ICPI	11.5±1.1 (9-13)	9.35±1.96* (5-12)	8.37±2.12*† (4-11)	9.05±1.88* (5-11)	65.5	<0.001
No of voids	18.0±5.7 (12-35)	14.0±4.44* (8-26)	12.9±3.8*† (7-25)	13.5±2.94* (8-22)	50.3	<0.001
Mean void volume (mL)	140.9±60.1 (45-255)	172.8±68.5* (70-345)	190.4±72.7*† (70-350)	183.3±64.6* (70-360)	17.9	<0.001
Urodynamics 1st sensation of urination (mL)	73.2±17.9 (40-100)			81.4±18.5 (40-110)	Paired "t"=7.07	<0.001 (HS)
Cystometric capacity (mL)	202.1±49.1 (120-300)			224.7±49.2 (130-340)	Paired "t"=16.7	<0.001 (HS)
Q-max (mL)	20.0±6.5 (10-35)			18.8±4.9 (12-35)	Paired "t"=0.94	0.35 (NS)

*→ significant in comparison to "Baseline"

† → significant in comparison to "2 weeks after ttt"

‡→ significant in comparison to "3 m after ttt"

Post hoc multiple comparisons using Bonferroni adjusted paired "t" test

ttt: treatment; VAS: visual analogue scale; ICPI: interstitial cystitis problem index; ICSI: interstitial cystitis symptom index; PUF: pelvic pain and urgency/frequency; Q-max: maximum flow rate

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CS 2.0% in 0.9% saline solution (IALURIL®) (IBSA, Lugano, Switzerland) once weekly for 8 weeks, then once every 2 weeks for the next 6 months and showed significant improvement with variable degrees in all patients regarding VAS scores, ICSI, ICPI, and PUF questionnaire scores, also, it showed decrease in mean number of voids and increase in mean voided volume. The mean period of follow up was six months after the last instillation. This study differs from our study in that we used only 8 instillations. Our reported results obtained at 2 weeks after the last instillation didn't differ greatly from their results which were reported at the 5th month of the follow-up period, but our results reported at 3rd months showed a much better improvement.

In 2008 Cervigni et al.[23] reported their results of intravesical CS/HA therapy in 23 IC/BPS patients, refractory to other methods of treatment. They used a combination of HA 1.6% and CS 2.0% over a period of 9 months, including 25 instillations, and assessing symptoms using a visual analogue scale, 3-day voiding diaries and previously mentioned questionnaires before and after the last dose within a mean period of 5 months. Their results appear to be near to the results recorded by Porru et al.[22] and near to our results obtained at 2 weeks after treatment but at 3 months after the last instillation the results improved greatly.

Giberti et al.[24] used (800 mg/50 mL) 1.6% of sodium HA and 2.0% CS but used only 9 instillations for 5 months and their reported results appear to be similar to our results. Also, we reported a sustained and progressive improvement in patient's symptoms at 3, and at 9 months after the last instillation. Our results reported at 9 months appear to be like those reported by Cervigni et al.[23] for the 9th month of the follow-up period.

There is only one reported study by Cervigni which assessed long-term response to treatment at 9 months and 3 years of the follow up period, and our results reported at 9 months showed much better improvement results in comparison to the results reported by Cervigni for the corresponding period.[25]

Regarding urodynamic changes in response to treatment, we found only one study by Cervigni et al.[23] in 2008 which considered urodynamic data to assess response to treatment and they reported minimal changes in urodynamic data which appeared to be statistically insignificant.
Our patients underwent complete urodynamic assessments before instillation and at 9 month after the last dose which showed significant increase in both 1 St sensation of urination, maximum cystometric capacity values when compared with those of the baseline.

Regarding the Q max there is no significant difference between the baseline and 9th month of the follow-up period. Our reported urodynamic results showed a very little difference from those reported by Cervigni et al.[23] This may be attributed to an extremely prolonged pretreatment period, and lack of a longer follow-up period required to record more prominent changes in urodynamic parametres.

In addition to the high efficacy of HA/CS, it was well tolerated by all patients with no recorded side effects during the study period except for urethral pain felt during catheterization. We considered some limitations in this work as a relative small number of patients and a relatively short follow-up period.

In conclusion, intravesical instillation with both HA/CS in the treatment of refractory painful bladder syndrome is safe, effective and well tolerated by all patients with no recorded side effect.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Benha Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept-H.S.; Design – A.S., T.O., A.M.; Supervision-A.S., H.S., W.K., A.E.; Data Collection and/or Processing – T.O., A.M., A.F., H.S.; Analysis and/or Interpretation – A.S., W.K., A.F.; Literature Search – A.E., T.S.; Writing Manuscript – T.O., H.S.; Critical Review – H.S., A.E.

Conflict of Interest: The authors have no conflicts of interest to declare.

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