DOI: 10.4081/aiua.2022.4.447

ORIGINAL PAPER

# Evaluation of pain and quality of life after hyaluronic acid instillation in addition to botulinum toxin-A injection in women with refractory Interstitial Cystitis/Painful Bladder Syndrome: A pilot study

**Ahmed Fayez Ghaith [1], Mohamed Hasan Radwan [1], Mohamed Rasheed Taha [1], Mohamed Ahmed Elbendary [1], Mahmoud Elsayed Al Damhogy [2], Ayman Mohamed Hagras [1]**

[1] Urology Department, Faculty of Medicine, Tanta University, Tanta, Egypt;
[2] Urology Department, Almogammaa Altebby Insurance Hospital, Tanta, Egypt.

**Summary**

***Objectives:*** *The aim of this study was to assess changes in quality of life and pain alleviation in women with refractory Interstitial Cystitis/Painful Bladder syndrome following a combined intravesical injection of Botulinum Toxin-A and Hyaluronic Acid instillation versus Hyaluronic acid instillation alone.*

***Methods:*** *Two groups of women with painful bladder syndrome/interstitial cystitis were randomly divided (one to one randomization). Intravesical injections of botulinum toxin-A and intravesical Hyaluronic acid were given to Group (I). Only Hyaluronic acid was instilled intravesically in Group II. Patients were given voiding diaries, a visual analogue scale for pelvic pain, the International Cystitis Symptom Index and Problem Index, the Pelvic Pain Urgency/Frequency Patient Symptom Scale, and the Patient Health Questionnaire-9 to assess the candidates' quality of life. The Student t-test and mean and standard deviation were used in statistical analysis, with p 0.05 considered as significant (IBM SPSS statistics)*

***Results:*** *Thirty-four women were included in this study. The pain severity (VAS) of group (I) cases dropped dramatically from 8.5 ± 1.5 at the start to 3.9 ± 2.4 after three months and 2.9 ± 2.1 after six months. Among group (II) cases, the pain score reduced dramatically from 8.6 ± 1.3 to 5.8 ± 1.4 to 4.3 ± 2.6.*

***Conclusions:*** *In patients with refractory Interstitial Cystitis/Bladder Discomfort Syndrome, Botulinum Toxin-A injection combined with Hyaluronic Acid instillation improves pelvic pain and improves quality of life.*

KEY WORDS: *Painful Bladder Syndrome; Botulin toxin; Hyaluronic acid.*

Submitted 5 November 2022; Accepted 19 November 2022

## INTRODUCTION

*Interstitial Cystitis/Bladder Pain Syndrome* (IC/BPS) is a condition presenting pelvic pain and urinary storage symptoms like as urgency and frequency that has no recognized cause (1).

The injury or dysfunction of the urothelium's *glycosaminoglycan* (GAG) layer caused by urine diffusion hypothetically leads to sensory nerve activation, mast cell stimulation, and bladder inflammation (2). *Hyaluronic acid* (HA) instillation intravesically in patients with IC/BPS may help to regenerate the GAG layer.

Furthermore, it appears that HA inhibits mast cell degranulation (3). After several weeks of weekly HA administration in the bladder, a significant reduction in symptoms was noted (1). Botulinum toxin-A, on the other hand, is an effective, well-tolerated, and safe therapy option for patients with ICS/PBS. It aids in the relief of pain and the treatment of bladder ulcers (3). The duration of botulinum toxin-A treatment is less than nine months, and 88 percent of cases require repeating injection (2). IC/BPS has a significant impact on patients' psychological well-being, including sleep disturbances, sadness, anxiety, and a poor quality of life (4). The goal of this study was to assess the improvement criteria and the improvements in quality of life for women with refractory IC/BPS who received a combined intravesical injection of Botulinum toxin-A with HA instillation.

## MATERIALS AND METHODS

Thirty-four adult women with refractory IC/BPS were prospectively considered in this pilot trial between January 2017 and January 2020.

### *Inclusion criteria*

Inclusion criteria were bothering urinary nocturia, frequency, urgency and pelvic pain not responding to oral medications for a period of 6 months or more.

### *Exclusion criteria*

Exclusion conditions were: pregnancy, malignancy, radiation cystitis, other urogenital diseases (e.g., congenital anomalies, infection, or stones) and bleeding disorders.

Gynecologic examination was done to exclude vaginal infection, prolapse, menopausal changes and endometriosis.

### *Randomization*

The cases were evenly randomized (one to one randomization) into two groups, each with 17 women. BTX-A

No conflict of interest declared.

was given to group (I) in addition to HA, while group (II) received only HA.

### *Procedures*

Routine laboratory testing and an abdominal-pelvic ultrasonography were performed on all women. To rule out any pathology, a cystoscopy with hydrodistension (using semi-rigid cystoscopy at a pressure of 80 to 100 cm $H_2O$ for 1 to 2 minutes and up to 2 times) was performed at least one month prior to enrolment. Bladder biopsies for suspected bladder granulations were performed in 11 instances. Group (I) received a sub mucosal intravesical injection of 200 units of *botulinum toxin-A* (BTX-A) in 20 locations of the superficial bladder muscles, including the trigone under spinal anesthesia. Intravesical instillation of 40 mg/50 ml of Hyaluronic acid was done every two weeks in all patients (groups I&II) for a total of twelve sessions. The HA was administered to group (I) two weeks following the BTX-A injection. After two weeks of HA implantation, patients were examined for any negative effects. Before and after 3 and 6 months of treatment, all patients completed voiding diaries for four days, the *International Cystitis Symptom Index* and *Problem Index* (ICSI & ICPI), the *Pelvic Pain Urgency/Frequency Patient Symptom Scale* (PUF), pelvic pain on a visual analogue scale (0-10 VAS), and the candidates' quality of life (PHQ-9).

### *Ethical approval*

Ethical approval was obtained from our local university ethical committee before enrollment (187/12/2016). Informed consent was obtained from the patients before enrollment with full knowledge of risks and benefits of the study.

### *Statistics*

The Student t-test and mean and standard deviation were used in statistical analysis, with p 0.05 considered significant (IBM SPSS statistics).

## Results

The survey was completed by 34 women, ranging in age from 37 to 63. Inflammatory and mast cell infiltration were seen in bladder samples of 11 patients. All patients completed the questionnaires before therapy, three months after treatment, and six months later. Treatment resulted in significant improvements in both groups as compared to pretreatment values (Table 1). The improvement in group (I) was greater than the improvement in group (II) (Table 1). The pain severity (VAS) of group (I) patients dropped dramatically from 8.5 ± 1.5 (pretreatment) to 3.9 ± 2.4 after 3 months and to 2.9 ± 2.1 after 6 months. Also, in group (II) patients, pain score (VAS) improved from 8.6 ± 1.9 (pretreatment) to 5.8 ± 1.4 at 3 months and to 4.3 ± 2.6 at 6 months. Furthermore, at 3 months (p = 0.041) and 6 months (p = 0.022), there was a substantial pain improvement (VAS) in group (I) cases (BTX-A+ HA) compared to group (II) women (Figure 1).

In group (I) women, their quality of life changed dramatically from 9.7 ± 2.3 (before treatment) to 6.9 ± 1.9 (3 months) and to 5.7 ± 1.5 after 6 months. PHQ-9 scores for group (II) patients changed from 9.8 ± 2.06 to 8.2 ± 1.8 and 7.9 ± 1.9 at 3 months and 6 months respectively. Patients in group (I) had a much higher quality of life than patients in group (II) (Figure 2).

***Table 1.***
*Reported data of the candidates of both groups: pre-treatment, at 3 months visit and 6 months post-treatment.*

| | Pre-treatment | 3 months post-treatment | 6 months post-treatment | P-value pre/6-months post-treatment | P-value Gp I/II 6 months post-treatment |
|---|---|---|---|---|---|
| VAS (Gp I) | 8.5 ± 1.5 | 3.9 ± 2.4 | 2.9 ± 2.1 | 0.009 | 0.022 |
| VAS (Gp II) | 8.6 ± 1.3 | 5.8 ± 1.4 | 4.2 ± 2.6 | 0.032 | |
| VV (Gp I) | 150.9 ± 26.4 | 185.6 ± 27.1 | 188.1 ± 39.9 | 0.002 | 0.019 |
| VV (Gp II) | 149.9 ± 27.9 | 162.8 ± 24.04 | 177.8 ± 26.5 | 0.033 | |
| Freq. (Gp I) | 16.05 ± 2.4 | 11.7 ± 2.2 | 10.4 ± 1.3 | 0.0002 | 0.001 |
| Freq. (Gp II) | 15.4 ± 2.5 | 12.9 ± 2.1 | 12.3 ± 2.02 | 0.010 | |
| ICSI (Gp I) | 15.4 ± 3.4 | 10.5 ± 2.6 | 7.41 ± 2.2 | 0.0007 | 0.0008 |
| ICSI (Gp II) | 15.7 ± 3.3 | 12.5 ± 2.9 | 11.1 ± 2.9 | 0.012 | |
| ICPI (Gp I) | 13.1 ± 2.7 | 7.8 ± 2.01 | 6.2 ± 2.03 | 0.007 | 0.009 |
| ICPI (Gp II) | 13.5 ± 2.5 | 9.5 ± 2.06 | 8.6 ± 1.8 | 0.036 | |
| PUF (Gp I) | 20.4 ± 3.1 | 13.8 ± 3.00 | 11.9 ± 2.6 | 0.0004 | 0.001 |
| PUF (Gp II) | 20.1 ± 3.4 | 16.8 ± 2.6 | 15.7 ± 3.06 | 0.001 | |
| PHQ (Gp I) | 9.7 ± 2.8 | 6.9 ± 1.9 | 5.7 ± 1.5 | 0.0007 | 0.0005 |
| PHQ (GP II) | 9.8 ± 2.06 | 8.2 ± 1.8 | 7.9 ± 1.9 | 0.020 | |

*ICSI: Interstitial cystitis symptom index; ICPI: Interstitial cystitis problem index; PHQ-9: Patient health questionnaire-9; PUF: Urgency/frequency patient symptom scale; VAS: Visual analogue scale; VV: Voiding volume.*

***Figure 1.***
*Visual analogue scale in both groups.*

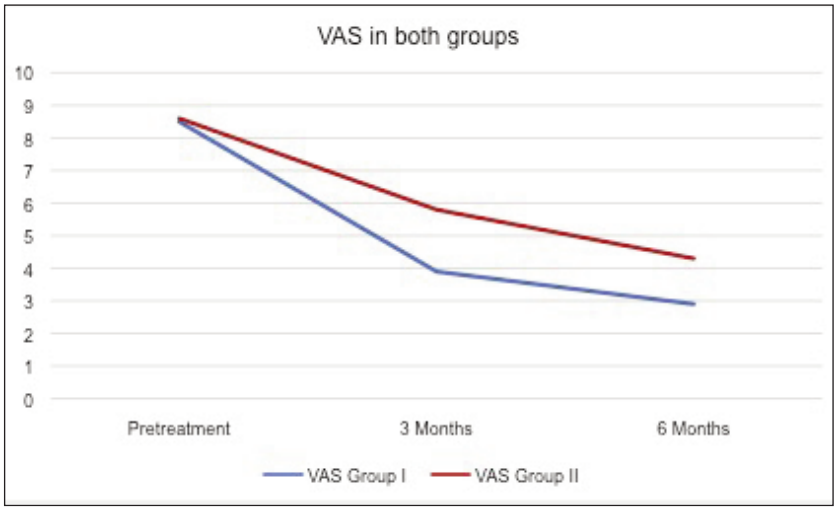
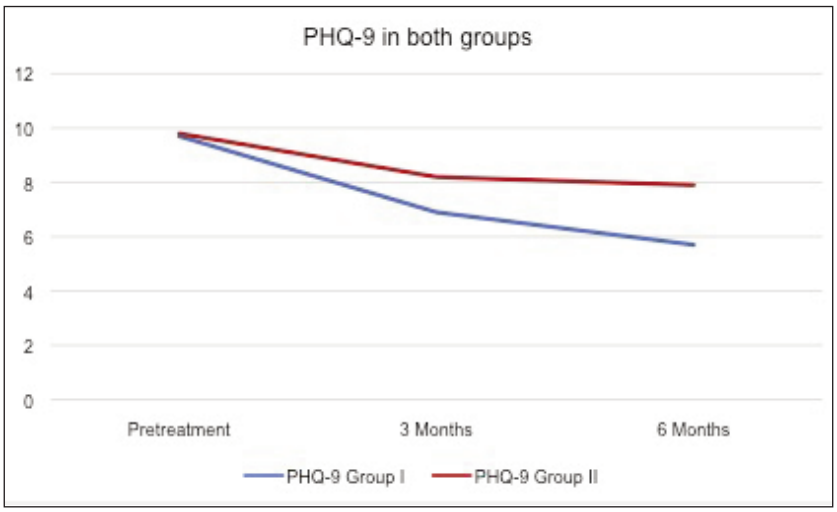


***Figure 2.***
*Health related quality of life in both groups.*




## Discussion

PBS/IC (painful bladder syndrome/interstitial cystitis) is a disorder characterized by supra-pubic and/or bladder pain associated with bladder filling, as well as urine frequency and urgency, which has a significant impact on quality of life (2, 5). Women are nine times more affected than men. Because the actual etiology is complex and multifactorial, no consistent treatment method exists (6). Infection, autoimmunity, defective urothelium, mast cell activation, neural inflammation, and other causes have all been suggested (7). The disruption of the *glycosaminoglycan* (GAG) layer, which covers the bladder epithelium and acts as an impermeable barrier to solutes, may play a key role in PBS/IC pathogenesis (8). Hydrated hyaluronic acid, heparin sulphate, dermatan sulphate, chondroitin sulphate, and keratin sulphate make up the GAG layer (9). Interstitial cystitis/bladder pain syndrome is linked to unfavorable cognitive, behavioral, and sexual outcomes, as well as bothersome urine symptoms (2). To address lower urinary tract symptoms, a variety of oral medications have been tried, including *pentosan polysulfate sodium* (PPS), tricyclic antidepressants, and anti-muscarinics. Intravesical therapy is commonly utilized as a second-line treatment for individuals who do not react to oral medication (3). Many studies looked at the effectiveness of HA or BTX-A alone, in conjunction with other medicines, or in combination with other techniques such hydrodistension. The results of adding BTX-A to HA versus HA alone were compared in this study. In patients with refractory IC/PBS, we got a better response when we combined the two medicines. BTX-A has been used to treat persistent pelvic pain, and preliminary results indicate that it is a safe therapeutic option with no severe side effects (10). Intravesical HA was examined in women with refractory interstitial cystitis by *Hung et al.* (1) in a prospective, multicenter study. After treatment, pain ICSI, VAS, and ICPI scores improved significantly in 103 individuals. However, patients' bladder discomfort and storage symptoms improved at various speeds (74 percent vs. 48 percent; respectively). Lower pain score and decreased bladder capacity were the characteristics that adversely affected treatment results, according to repeated statistical studies. In their randomized trial, *Kuo et al.* (11) enrolled 67 patients with refractory IC/PBS. In patients with refractory IC/PBS, they found that intravesical injections of BTX-A followed by HD had superior clinical results than HD alone. Later, *Kuo et al.* (12) In patients with IC/BPS, intravesical injections of BTX-A improved bladder pain symptoms. *Gao and Liao* (10) studied the efficacy of an intravesical injection of 100 U Chinese BTX-A followed by cystoscopic hydrodistension under general anesthesia in 124 women with IC/BPS. They concluded that intravesical injections of Chinese BTX-A were a safe and effective treatment for IC/BPS patients. Furthermore, *Smith et al.* (13) found that BTX-A had an anti-nociceptive impact on the bladder, improving both symptoms and urodynamics. *Akiyama et al.* (14) randomized 34 patients with refractory IC/BPS into two groups: group A received immediate BTX-A injections and group B received BTX-A injections one month later. They concluded that BTX-A injection could be an alternate treatment for refractory IC/BPS patients.

Furthermore, *Shim et al.* (15) demonstrated that BTX-A injection is more effective for IC/BPS pain control than placebo, with no differences in adverse effects. *Pinto et al.* (16) also concluded that trigonal BTX-A injection is a safe treatment for refractory BPS/IC. According to *Kim et al.* (17), the VAS score, mean changes in the PUF, ICSI, and ICPI all decreased significantly after 4 weeks of intravesical HA instillation. Furthermore, *Akbay et al.* (18) found that intravesical hyaluronic acid instillation alleviated symptoms in IC/BPS patients on a short-term follow-up. *Lai et al.* (4) compared four weekly 40 mg hyaluronic acid intravesical instillations followed by five monthly instillations to 12 intravesical instillations every two weeks. There was no significant difference between the two groups in terms of symptom scores or the Quality-of-Life Index. Furthermore, according to the findings of *Peng et al.* (19), enhanced first desire to void and maximum cystometric capacity are linked to improved urinary symptoms after HA treatment. *Cervigni et al.* (20) also looked at the efficacy of HA and *chondroitin sulphate* (CS) intravesical instillations in individuals with refractory PBS/IC. Pain and urine symptoms such as urgency ($p = 0.005$), frequency ($p = 0.045$), and pain ($p = 0.001$) improved significantly. In their meta-analysis, *Pyo and Cho* (21) found that intravesical HA and HA/CS instillation improved pain symptoms and quality of life in patients with IC/BPS. In individuals with IC/BPS, *Liang et al.* (22) found that pain and urine symptoms may improve after 6 months of intravesical HA therapy. There were no significant changes in the psychological and sexual functioning ratings at the time. *Lv and colleagues* (23), in women with refractory severe PBS/IC, demonstrated that intravenous instillation of HA and AL resulted in immediate and long-term allevi-

ation of symptoms. Hyaluronic acid intravesical instillation was successful in reducing the degree of pain in women with refractory PBS/IC in the current pilot trial. *Botulinum Toxin-A* added to *Hyaluronic acid* resulted in much higher quality of life and pain reduction than Hyaluronic acid alone. This is the only publication that we are aware of that discussing the advantages of combining HA with BTX-A injection for the treatment of IC/BPS.

***Limitations to the study***

A longer follow-up and larger number of patients should be considered in the upcoming studies.

## Conclusions

In patients with refractory *Interstitial Cystitis/Bladder Discomfort Syndrome*, *Botulinum Toxin-A* injection combined with *Hyaluronic Acid* instillation improves pelvic pain and improves quality of life.

## References


*1. Hung MJ, Tsai CP, Lin YH, et al. Hyaluronic acid improves pain symptoms more than bladder storage symptoms in women with interstitial cystitis. Taiwan J Obstet Gynecol. 2019; 58:417-422.*

*2. Hanno P, Lin A, Nordling J, et al. Bladder pain syndrome committee of the international consultation on incontinence. Neurourol Urodyn 2010; 29:191-198.*

*3. Garzon S, Laganà AS, Casarin J, et al. An update on treatment options for interstitial cystitis. Prz Menopauzalny 2020; 19:35-43.*

*4. Lai MC, Kuo YC, Kuo HC. Intravesical hyaluronic acid for interstitial cystitis/painful bladder syndrome: A comparative randomized assessment of different regimens. International Journal of Urology 2013; 20:203-207.*

*5. Wein AJ, Hanno PM. Targets for therapy of the painful bladder. Urology 2002; 59:68-73.*

*6. Jhang JF, Kuo HC. Novel Treatment of Chronic Bladder Pain Syndrome and Other Pelvic Pain Disorders by OnabotulinumtoxinA injection. Toxins (Basel). 2015; 7:2232-50.*

*7. Grover S, Srivastava A, Lee R, et al. Role of inflammation in bladder function and interstitial cystitis. Ther Adv Urol. 2011; 3:19-33.*

*8. Parsons CL. The role of the urinary epithelium in the pathogenesis of interstitial cystitis/prostatitis/urethritis. Urology 2007; 69:9-16.*

*9. Teichman JM, Moldwin R. The role of the bladder surface in interstitial cystitis/painful bladder syndrome. Can J Urol. 2007; 14:3599-607.*

*10. Gao Y, Liao L. Intravesical injection of botulinum toxin A for treatment of interstitial cystitis/bladder pain syndrome: 10 years of experience at a single center in China. Int Urogynecol J 2015; 26:1021-1026.*

*11. Kuo HC, Chancellor MB. Comparison of intravesical BTX-A injections plus HD with HD alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int. 2009; 104:657-61.*

*12. Kuo HC, Jiang YH, Tsai YC, Kuo Y. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment - A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. 2016; 35:609-6014.*

*13. Smith CP, Radziszewski P, Borkowski A, et al. Botulinum toxin A has antinociceptive effects in treating interstitial cystitis. Urology 2004; 64:871-875.*

*14. Akiyama Y, Nomiya A, Niimi A, et al. Botulinum toxin type A injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. Int J Urol. 2015; 22:835-41.*

*15. Shim SR, Cho YJ, Shin IS, Kim J. Efficacy and safety of botulinum toxin injection for interstitial cystitis/bladder pain syndrome: a systematic review and meta-analysis. Int Urol Nephrol. 2016; 48:1215-1227.*

*16. Pinto R, Lopes T, Frias B, et al. Trigonal Injection of Botulinum Toxin A in Patients with Refractory Bladder Pain Syndrome/Interstitial Cystitis. European Urology 2010; 58:360-365.*

*17. Kim A, Lim B, Song M, Choo M. Pretreatment Features to Influence Effectiveness of Intravesical Hyaluronic Acid Instillation in Refractory Interstitial Cystitis/Painful Bladder Syndrome. Int Neurourol J. 2014; 18:163-167.*

*18. Akbay E, Çayan S, Kılınç C, et al. The short-term efficacy of intravesical instillation of hyaluronic acid treatment for bladder pain syndrome/interstitial cystitis. Turk J Urol. 2019; 45:129-34.*

*19. Peng YC, Chiu SY, Feng M, Liang C. The effect of intravesical hyaluronic acid therapy on urodynamic and clinical outcomes among women with interstitial cystitis/bladder pain syndrome. Taiwan J Obstet Gynecol. 2020; 59:922-926.*

*20. Cervigni M, Natale F, Nasta L, et al. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int Urogynecol J. 2008; 19:943-947.*

*21. Pyo JS, Cho WJ. Systematic Review and Meta-Analysis of Intravesical Hyaluronic Acid and Hyaluronic Acid/Chondroitin Sulfate Instillation for Interstitial Cystitis/Painful Bladder Syndrome. Cell Physiol Biochem. 2016; 39:1618-1625.*

*22. Liang CC, Lin YH, Hsieh WC, Huang L. Urinary and psychological outcomes in women with interstitial cystitis/bladder pain syndrome following hyaluronic acid treatment. Taiwanese Journal of Obstetrics & Gynecology 2018; 57:360-363.*

*23. Lv Y, Zhou H, Mao H, et al. Intravesical hyaluronic acid and alkalinized lidocaine for the treatment of severe painful bladder syndrome/interstitial cystitis. Int Urogynecol J. 2012; 23:1715-1720.*



**Correspondence**

*Ahmed Fayez Ghaith, MD (Corresponding Author)*
dr_ahmedfayez@yahoo.com

*Mohamed Hasan Radwan, MD*
drradwanm@yahoo.com

*Mohamed Rasheed Taha, MD*
dr-rasheed@hotmail.com

*Mohamed Ahmed Elbendary, MD*
mbendary@hotmail.com

*Ayman Mohamed Hagras, MD*
ahagras80@yahoo.com

Urology Department, Faculty of Medicine, Tanta University, Tanta (Egypt)
El-Gharbia Govenorate, Tanta. El-Gash st. Medical Campus, The Faculty of Medicine

*Mahmoud Elsayed Al Damhogy, MD*
moodseg@gmail.com

Urology Department, Almogammaa Altebby Insurance Hospital, Tanta (Egypt)