#489 Lessons learned from using intravesical hyaluronic acid for treatment of refractory interstitial cystitis in Taiwan: A systematic review

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Aims of Study

Interstitial cystitis (IC) is a chronic bladder disease which is characterized by pelvic pain, urinary frequency, and urgency in the absence of other identifiable pathology such as urinary tract infection or cancer. The precise mechanism and pathophysiology remain poorly understood and potential causes include infection, autoimmune processes, neuronal inflammation, exposure to toxins, psychosomatic factors, detrusor fibrosis, and damage to the glycosaminoglycan (GAG) layer of the bladder urothelium. Many studies have shown that a subset of IC/BPS patients have a documented defect of the GAG layer in the bladder mucosa which has led to a variety of intravesical instillation medications such as hyaluronic acid (HA), chondroitin sulfate and pentosane polysulphate being utilized to restore the GAG layer and treat IC/BPS. Hyaluronic acid is a key component of GAG and bladder instillation of HA has become an acceptable treatment option to repair the GAG layer in IC/BPS patients. Though widely used as a treatment modality, previous studies have shown varying degrees of success in treatment outcomes which may likely be due to differing outcome measures and patient population reported in each study. Intravesical HA therapy is reimbursed by the national health insurance in Taiwan for cystoscopic IC refractory to conventional treatment after prior review. The aim of this study was to conduct a systematic review of studies using intravesical HA instillations for the treatment of IC/BPS in Taiwan to determine the efficacy and safety of this treatment modality.

Methods

This study was designed and conducted in accordance with the PRISMA 2020 statement. EMBASE, PubMed, and The Cochrane Library were searched from inception until December 2023 to identify relevant studies. The search strategy included a combination of the following keywords: interstitial cystitis/bladder pain syndrome (IC/BPS), interstitial cystitis (IC), bladder pain syndrome (BPS), painful bladder syndrome, intravesical treatment, hyaluronic acid (HA), and Taiwan. Articles were considered for inclusion if they were studies evaluating the effectiveness of intravesical hyaluronic acid instillations on interstitial cystitis/bladder pain syndrome in Taiwan. There was no restriction on type of study or clinical outcomes reported in the study. Articles were excluded if they were studies of non-human subjects, or in vitro studies; studies with data not reliably extracted, duplicate, or overlapping data; abstract-only papers as preceding papers, conference, editorial, and author response theses and books; articles without full text available; or case reports, case series, and systematic review studies. The main outcomes of interest included the response rate, pain-VAS scores, and changes in urodynamic parameters.

Results

Eight articles were identified and study characteristics were presented in Table 1. The eight studies recruited a total of 427 participants with IC/BPS and included one randomized control trial, two multicenter prospective cohort studies, three single-site prospective cohort studies, one retrospective single-site cohort study and one secondary analysis of a multicenter prospective cohort study. All were diagnosed via the guidelines published either by the ESSIC or the East Asian guidelines. The most commonly used HA instillation regimen was that of four weekly bladder instillations, each with 40mg/50mL of a commercial HA solution followed by five monthly bladder instillations for a total treatment time of six months. All studies found a statistically significant decrease in pain, ICSI, and ICPI scores post-HA treatment. Studies that included analysis of global response assessments (GRA) on bladder pain, bladder storage and overall bladder conditions showed moderately or markedly improved symptoms in the majority of patients after HA treatment. Five studies found statistically significant decreases in frequency and nocturia accompanied with statistically significant increases in bladder capacity. Interestingly, studies found no differences in urgency after HA treatment. Four studies included urodynamic studies with results varying between studies with the majority of studies finding no statistically significant differences post-HA treatment in parameters such as voided volume, postvoid residual, residual urine, and maximum flow rate. Of the three studies which included data on sexual function, two studies found significant increases in PISQ scores at 1-month and 6-month follow-up when compared to baseline with significant improvements in the three parameters of dyspareunia, negative reactions and intensity of orgasms.

Interpretation of Results

Studies found statistically significant decreases in frequency and nocturia accompanied with statistically significant increases in bladder capacity. On average, the bladder capacity increased by 43.3 mL at six-months follow-up after hyaluronic acid instillation. These findings correlated well with those of previous reviews which also found improvements in bladder capacity and voiding frequency post-HA treatment. Clinical parameters including pain, ICSI, and ICPI scores all had statistically significant changes post-HA instillation. There was a statistically significant decrease in ICPI and ICSI scores along with an average decrease of 2.11 points in the pain-VAS between baseline and six-months post-treatment. These decreases in pain-VAS, ICSI, ICPI and GRA were all able to be sustained for at least six months with one study showing decreases sustained for up to nine months after the last HA instillation. However, one study noted that while there was a clear decrease in average pelvic pain scores in patients pre- and post-treatment, a high percentage of patients still reported a mild or greater pelvic pain after treatment. These findings are consistent with previous studies which found marked improvements in pain scores post-treatment but that a certain subset of patients would still have lingering symptoms so continued instillation as a maintenance therapy is warranted to control the pain symptoms. This further proves that IC/BPS is a chronic disease and most patients need maintenance therapy to achieve a satisfactory quality of life.

Previous studies have shown that the tolerability of the intravesical hyaluronic acid instillation therapy is high and the rate of adverse effects is low. Of the 427 participants included in this review, there were no drop-outs due to intolerability of the instillation regimen and there were no reported serious adverse effects or complications related to the treatment. These experiences indicated that intravesical HA therapy is a safe and tolerable treatment regimen for IC/BPS patients.

Author	Study Design	Patients	Intervention	Follow-up Time	Outcomes Measured	Main Outcomes
Lai et al.	Randomized control trial	16-77 years old (n = 59)	Group 1: 30 patients received weekly 40mg/50mL HA followed by 5 monthly instillations (HA-5) Group 2: 30 patients received biweekly 40mg/50mL HA for 12 weeks (HA-12)	Baseline, 1-month, 3-month, and 6-month	1. Urodynamic parameters 2. 3-day voiding diary 3. ICSI / ICPI 4. Pain - VAS 5. GRA of bladder symptoms	ICSI, ICPI, and total score, pain VAS, functional bladder capacity, Qmax and QOL-I improved significantly by 6 months in both groups
Jiang et al.	Prospective	16-61 years old (n = 33)	Weekly 40mg/50mL HA for 4 weeks then monthly for 5 months	Baseline and 6-months	1. Urine samples (Urinary NGF and BDNF) 2. Pain - VAS 3. 3 day voiding diary 4. GRA of bladder symptoms	1. After 6-months of treatment, urinary NGF and NGF/Cr levels both decreased significantly while urinary BDNF and BDNF/Cr levels did not 2. Clinical assessments (VAS, GRA, FBC) all significantly improved after treatment
Hung et al.	Prospective, multicenter	22-69 years old (n = 103)	Weekly 40mg/50mL HA for 4 weeks then monthly for 5 months	Baseline, 1-month, and 6-month	1. PISQ-9 2. ICSI / ICPI 3. Pain - VAS	All clinical parameters (pain-VAS, ICSI, ICPI, PISQ-9) were significantly improved after 1 month and 6 months of treatment
Liang et al.	Prospective	25-71 years old (n = 30)	Weekly 40mg/50mL HA for 4 weeks then monthly for 5 months	Baseline, 1-month, 6-month, and 9-month	1. 3-day voiding diary 2. HADS 3. ICSI / ICPI 4. PISQ-12 5. Pain - VAS	1. All clinical parameters were improved 6 months after HA treatment and sustained up to 9 months after HA treatment 2. IC patients had a decrease in HADS scores and an increase in PISQ-12 score after HA treatment but there was no significant differences in both scores between pre- and post-treatment
Hung et al.	Secondary analysis of a prospective, multicenter study	22-69 years old (n = 103)	Weekly 40mg/50mL HA for 4 weeks then weekly for 5 months	Baseline, 1-month and 6-month	1. Urodynamic Study 2. ICSI / ICPI 3. GRA of bladder pain symptoms 4. Pain - VAS	1. Significant improvement in bladder pain, urinary symptoms and bother were noted after one month and six month treatment 2. HA was more effective in improving bladder pain than storage symptoms
Peng et al.	Retrospective	32-64 years old (n = 30)	Weekly 40mg/50mL HA for 4 weeks then monthly for 5 months	Baseline and 3-months	1. 3-day voiding diary 2. ICSI / ICPI 3. Pain and Urgency - VAS 4. Urodynamic study	Urinary symptoms, VAS pain and urgency, ICSI, and ICPI scores were significantly improved after HA
Tsai et al.	Prospective, multicenter	24-77 years old (n = 137)	Weekly 40mg/50mL HA for 4 weeks then monthly for 5 months	Baseline, 1-month, and 6-month	1. Pain - VAS 2. ICSI / ICPI 3. PISQ-12 4. 3-day voiding diary 5. Urodynamic study 6. Cystoscopic findings	Improvements in both pain-VAS and ICSI and ICPI scores were detected soon after the initial 4 weekly instillations. Further significant improvements were found at the end of the 6-month treatment period
Lin et al.	Retrospective	18-68 years old (n = 35)	Weekly 40mg/50mL HA for 4 weeks then weekly for 5 months	Baseline, 1-month, and 6-month	1. Cystoscopic findings 2. Pain - VAS	Most of the grades of glomerulations remained unchanged despite HA treatment or even worsened

Conclusions

Intravesical hyaluronic acid instillation, which is a glycosaminoglycan layer replenishment therapy, is a safe and effective treatment option for patients with IC/BPS. Based on the study results in Taiwan, intravesical HA therapy can significantly improve bladder pain, lower urinary tract symptoms, urodynamic parameters and also improve the sexual function of female patients. However, the treatment has its limitations since there is a notable population of non-responders and those responders would still have lingering symptoms. Additional treatment such as pelvic floor physical therapy, oral medications, Botox injection and sacral neuromodulation may further benefit IC/BPS patients. Further studies are necessary to identify the ideal management modality for these patients.

References

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