Amniotic bladder therapy: six-month follow up treating interstitial cystitis/bladder pain syndrome

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CONSIDINE J, O'HOLLAREN K, RADOIU C, MADAN R, LIAW A, DHAR N. Amniotic bladder therapy: six-month follow up treating interstitial cystitis/bladder pain syndrome. *Can J Urol* 2024; 31(3):11898-11903.

Introduction: *Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by chronic pelvic pain and usually accompanies lower urinary tract symptoms. We have previously reported that amniotic bladder therapy (ABT) provides symptomatic improvement in refractory IC/BPS patients for up to 3 months. Herein, we evaluated the durability of ABT up to 6 months.*

Materials and methods: *Consecutive IC/BPS patients received intra-detrusor injections of 100 mg micronized amniotic membrane. Clinical evaluation and patient-reported outcome measurements including Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS) and Overactive Bladder Assessment Tool (OAB) were assessed.*

Results: *Twenty-five consecutive recalcitrant IC/BPS patients were included in the study with an average age of 47.4 ± 14.4 years (29-67 years). After ABT, the IC/BPS symptoms improved gradually up to 3 months in all patients with an average improvement in ICSI, ICPI, BPIC-SS and OAB score of 72.8%, 71.9%, and 66.6%, ($p < 0.001$) respectively, at 3 months. At 4 months after ABT, 7 patients experienced a rebound in symptoms and requested another injection which resulted in a significant improvement in IC/BPS symptoms after 2, 4, and 8 weeks ($p < 0.01$). For the 18 patients who received only one injection, the IC/BPS symptoms were still significantly lower at 5 and 6 months compared to baseline ($p < 0.01$), suggesting a possible durable effect based on the ICSI, ICPI, BPIC-SS, and OAB questionnaire scores.*

Conclusions: *ABT provided an improvement in pain and lower urinary tract symptoms up to 6 months post-treatment in some refractory IC/BPS patients.*

Key Words: amniotic, bladder pain syndrome, interstitial cystitis, intravesical therapy, lower urinary tract symptoms, painful bladder syndrome

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is characterized by chronic pelvic pain provoked by bladder filling and usually accompanies lower urinary tract symptoms such as frequency, urgency, and nocturia.[1] Unfortunately, the current conventional drugs and alternative surgical interventions have shown suboptimal therapeutic effects. The etiology and pathophysiology of IC/BPS are complicated and not well understood, but many studies have suggested that inflammatory and fibrotic changes in the bladder wall as well as urothelial dysfunction may play a role.[2] Therefore, for successful future treatment of patients with IC/BPS, it would be beneficial to discover and evaluate the therapeutic effects of compounds that can modulate IC/BPS-related inflammation, fibrosis, and urothelial damage.

Accepted for publication May 2024

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Our study hypothesis is as follows: if IC/BPS bladders present with increased inflammation, fibrosis, and urothelial dysfunction then treatment modalities that modulate inflammation and fibrosis and create a regenerative urothelial environment may have a therapeutic effect in such patients. One such potential treatment modality is human amniotic membrane (AM), which is a biological tissue known to contain anti-inflammatory and anti-scarring properties that are favorable for promoting a regenerative wound healing environment.[3,4] AM has been shown to promote apoptosis of activated neutrophils, promote polarization of macrophages to an anti-inflammatory phenotype characterized by increased expression of IL-10, and promote active phagocytosis of dead immune cells.[3-5] This anti-inflammatory and anti-scarring effect may allow for healing of the mucosal lining of the bladder as well as reduce the excitability of bladder afferent nerves induced by the inflammation.

The clinical utility and benefits of AM has been demonstrated in numerous applications including ocular surface reconstruction, osteoarthritis, lower extremity neuropathy, and chronic dermal wound healing.[6-9] More recently, we have reported that intra-detrusor injection of AM (i.e. amniotic bladder therapy, ABT) improved voiding symptoms and decreased bladder pain in patients with refractory IC/BPS at 3 months.[10,11] The pilot study demonstrated benefit of ABT in those patients for up to 3 months, however it remained unknown if there was a longer term benefit and if patients would eventually require re-treatment. Hence, in this current study, we evaluated the potential therapeutic effects at 6 months after ABT in patients with refractory IC/BPS.

Materials and methods

The patients enrolled in this study were affected by refractory bladder pain and urgency frequency syndrome, in the presence of sterile urine. The study was approved by the local institutional review board committee and all patients gave their written informed consent. We excluded patients with concomitant bladder outlet obstruction, prior radiotherapy, intravesical stones and history of bladder and pelvic cancer. Previous treatment modalities, including oral and intravesical therapies, have failed in all patients. Specifically, these failed treatments consisted of anticholinergics, antidepressants, antihistamines, bladder hydrodistention, pentosan polysulfate and intravesical bladder instillations.

Baseline evaluation included history, physical examination, serum chemistries, urinalyses, urine culture, urine cytology, post-void residuals, cystoscopy, and symptom assessments as measured by questionnaires of Bladder Pain/Interstitial Cystitis Symptom Score (BPIC-SS), Overactive Bladder (OAB) Assessment Tool, O'Leary/ Sant Voiding and Pain Indices (Interstitial Cystitis Symptoms Index (ICSI) and Interstitial Cystitis Problem Index (ICPI)).

Under general anesthesia, patients were given injections of 100 mg (for initial injection) or 200 mg (for those who had a second injection) of commercially available micronized AM diluted in 10 mL of 0.9% preservative-free sodium chloride. Injections were performed through a cystoscope using a 23-gauge Williams needle, intradetrusor into the lateral and posterior bladder wall, sparing the dome (to avoid intraperitoneal injection) and the trigone (because of the possible risk of reflux). Clinical evaluation and questionnaires were repeated at 2, 4, 8, 12, 16, 20, 24 weeks, and additional urine culture and post-void residuals were repeated at 2 and 4 weeks. Local or systemic side effects were noted during and after treatment. Patients were instructed to use acetaminophen (Tylenol) or phenazopyridine (Pyridium) as needed for any post-injection discomfort.

Descriptive statistics for continuous variables are reported as the mean ± SD and statistical analysis was performed using MiniTab (Minitab Inc., State College, PA, USA). Differences between parameters before and after treatment were analyzed with Wilcoxon Signed Rank Test. A p value < 0.05 was considered statistically significant.

Results

Twenty-five consecutive patients were included in the study with an average age of 47.4 ± 14.4 years (29-67 years). The patients suffered from IC/BPS for a median duration of 7.8 years (5.2-12.1 years) and had failed multiple therapies including anti-cholinergic (n = 25), beta-3 adrenergic agonist (n = 25), tricyclic anti-depressant (n = 25), anti-histamine (n = 5), hydrodistension (n = 25), pentosan polysulfate (n = 9), vaginal valium (n = 25), intravesical instillation (n = 8), botulinum toxin (Botox) injection (n = 25), and neuromodulation (n = 5). The patients had severe symptoms of IC/BPS as suggested by an ICSI score of 21.0 ± 0.2, ICPI score of 16.0 ± 0, BPIC-SS score of 36.5 ± 2.6, and OAB score of 23.8 ± 1.7. Injection of micronized AM was performed uneventful in all cases. All patients reported use of acetaminophen and/or phenazopyridine up to 36 hours post-injection, attributed to the injection itself.

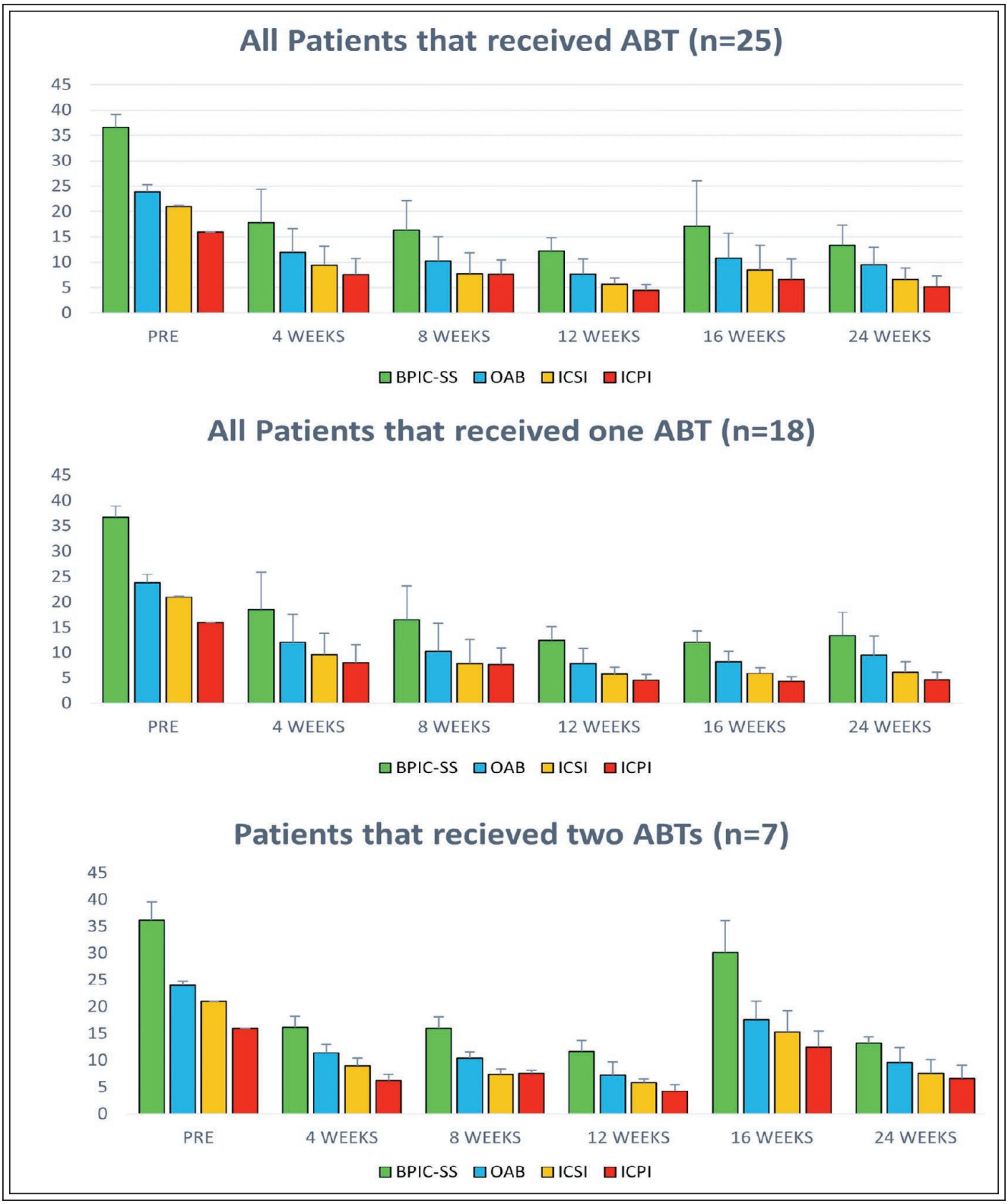

Figure 1. Questionnaire scores (average) by weeks. BPIC-SS = Bladder Pain/Interstitial Cystitis Symptom Score; OAB = Overactive Bladder Assessment Tool; ICSI = Interstitial Cystitis Symptom Index; ICPI = Interstitial Cystitis Problem Index.

TABLE 1. **Questionnaire scores before and after (± SD)**

All patients that received ABT (n=25)								
Questionnaire	**PRE**	**2 Wks**	**4 Wks**	**8 Wks**	**12 Wks**	**16 Wks**	**20 Wks**	**24 Wks**
BPIC-SS	36.5 ± 2.6	23.2 ± 5.8	17.84 ± 6.5	16.4 ± 5.8	12.2 ± 2.6	17 .2 ± 8.9	13.5 ± 2.3	13.4 ± 4.0
OAB	23.9 ± 1.45	15.2 ± 4.1	11.92 ± 4.7	10.2 ± 4.8	7.6 ± 2.9	10.8 ± 4.9	9.6 ± 2.9	9.5 ± 3.5
ICSI	21.0 ± 0.2	12.3 ± 4.0	9.4 ± 3.5	7.7 ± 4.1	5.72 ± 1.2	8.5 ± 4.8	6.8 ±3.2	6.6 ± 2.3
ICPI	16.0 ± 0	10.16 ± 2.4	7.5 ± 3.2	7.6 ± 2.8	4.5 ± 1.1	6.6 ± 4.0	5.5 ± 3.3	5.2 ± 2.1
Patients that received only One injection (n=18)								
Questionnaire	**PRE**	**2 Wks**	**4 Wks**	**8 Wks**	**12 Wks**	**16 Wks**	**20 Wks**	**24 Wks**
BPIC-SS	36.7 ± 2.3	23.6 ± 6.6	18.5 ± 7.6	16.5 ± 6.9	12.4 ± 2.8	12.1 ± 2.3	13.2 ± 2.4	13.4 ± 4.8
OAB	23.8 ± 1.7	15.3 ± 4.6	12.1 ± 5.6	10.1 ±5.8	7.8 ± 3.2	8.2 ± 2.1	8.8 ± 2.1	9.4 ± 3.9
ICSI	21.0 ± 0.2	12.8 ± 4.6	9.6 ± 4.4	7.8 ± 5.0	5.7 ± 1.4	5.9 ± 1.1	5.8 ± 1.7	6.2 ± 2.0
ICPI	16.0 ± 0	10.6 ± 2.7	8.0 ± 20.2	32.3 ± 3.4	4.6 ± 1.1	4.3 ± 0.8	4.2 ± 1.3	4.7 ± 1.6
Patients that received another injection after 16 weeks (n=7)								
Questionnaire	**PRE**	**2 Wks**	**4 Wks**	**8 Wks**	**12 Wks**	**16 Wks**	**20 Wks**	**24 Wks**
BPIC-SS	36.1 ± 3.6	22.3 ± 3.9	16.1 ± 2.2	16.0 ± 2.3	11.7 ± 2.1	30.1 ± 6.5	14.3 ± 2.3	13.3 ± 1.3
OAB	24.0 ± 0.8	14.7 ± 3.1	11.4 ± 1.7	10.4 ± 1.3	7.3 ± 2.6	17.6 ± 3.7	11.4 ± 4.2	9.6 ± 3.0
ICSI	21.0 ± 0	11.0 ± 1.7	9.0 ± 1.5	7.4 ± 1.0	5.9 ± 0.7	15.3 ± 4.3	9.3 ± 4.8	7.6 ± 2.8
ICPI	16.0 ± 0	9.0 1.6	6.3 ± 1.3	7.6 ± 0.5	4.3 ± 1.3	12.4 ± 3.2	8.7 ± 4.8	6.6 ± 2.7

After ABT, the IC/BPS symptoms improved gradually up to 3 months in all patients, Figure 1. The average improvement in ICSI, ICPI, and BPIC-SS score was 72.8% ($p < 0.01$), 71.9% ($p < 0.01$), and 66.6% ($p < 0.01$), respectively, at 3 months compared to before injection. The OAB score also significantly improved from 23.9 ± 1.45 at baseline to 7.6 ± 2.9 at 3 months ($p < 0.01$), corresponding to an improvement of 68.2%, Table 1.

At 4 months after ABT, the majority of patients continued to experience improvement in their IC/BPS symptoms based on the ICSI, ICPI, OAB, and BPIC-SS questionnaire scores, Table 1. However, 7 patients requested an additional injection of ABT due to recurrent IC/BPS symptoms (n = 7). For those 7 patients, the average ICPI score worsened from 4.3 ± 1.3 at 3 months to 12.4 ± 3.2 at 4 months ($p < 0.01$) and the ICSI score worsened from 5.9 ± 0.7 at 3 months to 15.3 ± 4.3 at 4 months ($p < 0.01$). The magnitude of improvement after the second injection was similar to the improvement seen after the initial injection suggesting consistent benefit to the patient. For example, the OAB score improved an average of 45.5% at 8 weeks after the second injection and improved 56.7% at 8 weeks after the first injection, Figure 1.

For the 18 patients that received only one injection, the IC/BPS symptoms were still significantly lower at 5 and 6 months compared to baseline, suggesting a possible durable 6 month effect based on the ICSI, ICPI, BPIC-SS, and OAB questionnaire scores, Figure 1. The change in scores between 4 weeks and 5 to 6 months was also insignificant ($p > 0.05$), suggesting the symptoms were not significantly recurring in those patients. Additionally, no adverse events related to micronized AM injections, such as UTIs or acute urinary retention, occurred throughout the current study.

Discussion

IC/BPS is considered a multifactorial disease with a complex pathobiology ultimately leading to chronic inflammation, bladder fibrosis and urothelial tissue injury.[2] We should also understand that IC/BPS is known to have multiple possible etiologies, many of which do not involve just the bladder. A study done by the MAPP research network categorized IC/BPS patients by pain distribution (widespread, intermediate, and local pelvic pain), noting that patients with widespread pain behave differently than those with local pelvic pain.[12] It should also be acknowledged that a bladder biopsy study by the NIH's ICDB (Interstitial cystitis database study) project found that only a small number of biopsies from IC patients had considerable inflammation, implying that IC/BPS may not always be a condition that mainly affects the bladder.[13] This underscores the importance of considering systemic factors and widespread pain in the management and study of IC/BPS.

Unfortunately, with traditional IC/BPS therapy, there is a greater attention on the treatment of symptoms experienced by the patient rather than treatment of the causes that underlie the pathophysiology of IC/BPS. Targeted symptom treatments have mixed outcomes, since the mechanisms are complex, and the complicated symptoms are not easy to control. The intractable nature of IC/BPS has typically led physicians to use a combination of various substances to maximize therapeutic effects. This exposes patients to multiple side effects and a higher possibility of drug toxicity, resulting in treatment dissatisfaction and a potentially higher discontinuation rate. To overcome such limitations, identification of alternative therapies that regulate bladder inflammatory and fibrotic processes and assist in the healing of bladder mucosal injuries may provide new options for IC/BPS patients.

In considering the potential for ABT to relieve IC/BPS, one must define the therapeutic basic science and clinical concepts behind deployment of AM for modulating the inflammatory and fibrotic processes as well as creating a favorable environment for promoting bladder tissue repair. AM is known to reduce inflammation by promoting cell death of activated, pro-inflammatory neutrophils, but not resting cells. Further, it promotes polarization of pro-inflammatory macrophages into an anti-inflammatory phenotype that have increased expression of anti-inflammatory cytokines.[5,14] Such effects prevent complete immune suppression yet modulate the local environment and allow the transition from a chronic inflammation to (epithelial and endothelial) cell proliferation and maturation. This would potentially be beneficial in treating IC/BPS, which has shown varying degrees of immune cells infiltrated into the bladder and increased inflammatory cytokines in the urine.[15] AM has also been shown to promote epithelial cell attachment, proliferation and migration, which is important for healing and closing the bladder mucosa after injury, thereby also preventing noxious stimuli from triggering the afferent nerves to fire.[16] The ability to promote normal epithelial and fibroblast proliferation and differentiation is important for preventing further inflammation and maintaining proper monitoring of bladder filling and composition of the urine.[17] Hence, AM's anti-scarring properties may prevent fibrosis, which can decrease bladder compliance and capacity leading to dysfunctional voiding.[3,16] These collective properties of anti-inflammation, anti-scarring, and promoting epithelial cell adhesion and proliferation may allow for regeneration of the damaged mucosal lining of the bladder in patients with IC/BPS and lead to symptomatic improvement.

We have previously reported that ABT could be an innovative treatment option for IC/BPS patients in terms of improving clinical symptoms based on preliminary outcomes at 3 months.[10,11] The main goal of the current study was to determine ABT 6 month durability on our cohort of 25 patients. As demonstrated, most patients continued to experience improvement in their IC/BPS symptoms at 4 months after treatment, while 7 patients experienced a rebound in symptoms. There were no significant factors or variables that we could identify that lead to the disparity between the 2 groups as they all had similar baseline symptom scores, prior treatments, void residuals, and cystoscopic findings. The seven patients initially received 100 mg intra-detrusor injection of AM, but requested another course of ABT which was delivered at a dose of 200 mg. The decision to increase the dose on re-injection was based on prior studies conducted with micronized AM including a dose-effectiveness response study in patients with plantar fasciitis and safety up to at least 300 mg in patients with pressure ulcers.[18,19] In the 7 patients, the injection procedure was carried out using the similar initial procedure and was demonstrated to have similar safety (no adverse events or complications) and effectiveness profile. As mentioned, the OAB score improved an average 45.5% at 8 weeks after the second (200 mg) injection and improved 56.7% at 8 weeks after the first (100 mg) injection ($p < 0.01$). Therefore, there may not be a similar dose-response using AM in IC/BPS as seen in plantar fasciitis, or the maximal effect can be achieved with 100 mg by which additional concentrations will not change the effect (e.g. steady-state concentration). Further studies are also needed to determine if the subsequent injection leads to a prolonged, similar, or decreased duration of effect compared to the initial injection. As seen with intradetrusor injection of onabotulinumtoxin A, the formation of neutralizing antibodies after repeated injections could occur in 5%-25% of patients, thereby leading to treatment failure or reduced effectiveness after repeated injection.[20,21]

The present study is a preliminary investigation employing an innovative approach that can be considered as a proof-of-concept intervention. The limitations of our study are its use of convenience sampling of a small group to evaluate the effectiveness of AM in patients with IC/BPS who were non-responders to conventional treatment. We report that the main limitations of this research include a single site and small sample size. Furthermore, there was no control group and there could be a potential placebo effect. The lack of assessment for widespread pain in

our study is also a significant limitation. Widespread pain has been shown to impact treatment efficacy in IC/BPS patients, with those experiencing more generalized pain potentially requiring different therapeutic approaches.[12] Future studies should include comprehensive pain assessments to better stratify patients and tailor treatments accordingly. Clinical investigations with a larger number of patients, through randomized clinical trials with a control and a sham group, and including histopathology, cystoscopy, urinary cytokines, biopsy, and molecular pathogen analysis patterns should be carried out to determine the possible AM mechanisms of action in IC/BPS. □

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