Advances in intravesical therapy for bladder pain syndrome (BPS)/interstitial cystitis (IC)

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Bladder pain syndrome (BPS)/interstitial cystitis (IC) is a chronic symptom complex that may cause bothersome storage symptoms and pain or discomfort of the bladder, adversely affecting a patient’s quality of life. The etiology of IC/BPS remains unclear, and its cause may be multifactorial. Diagnosis of IC/BPS is based on clinical features, and the possibility of other conditions must be ruled out first. Although no definitive treatment is currently available for IC/BPS, various intravesical therapies are used for IC/BPS, including heparin, hyaluronic acid, chondroitin sulfate, pentosan polysulfate, dimethylsulfoxide, liposomes, and botulinum onabotulinumtoxinA (BoNT-A). This review summarizes the intravesical therapy for IC/BPS and discusses recent advances in the instillation of liposomal-mediated BoNT-A and other newly developed intravesical therapies.

KEYWORDS
bladder pain syndrome, interstitial cystitis, intravesical therapy

1 INTRODUCTION

Bladder pain syndrome/interstitial cystitis (IC/BPS) is still a “mystery disease” in urology. Most urologists believe that there are different causes of IC/BPS, all result in a common outcome. Before making a diagnosis, physicians should rule out diseases that may cause similar symptoms, such as bladder inflammation, bladder malignancy, urinary tract stones, urinary tract obstruction, and overactive bladder (OAB). The pathogenesis of IC/BPS remains unclear, with different hypotheses proposed, such as dysfunction of the superficial layer of the extracellular matrix of the glycosaminoglycan (GAG) layer, downregulation of tight junction proteins, increased urothelial permeability, mast cell activation, neurogenic inflammation, and psychosomatic factors. Although oral treatment, such as with pentosan polysulfate sodium (PPS) (Elmiron; Jassen, NJ), hydroxyzine hydrochloride, tricyclic antidepressants (including amitriptyline HCL and imipramine), and anticholinergics, has been used to relieve the lower urinary tract symptoms, intravesical therapy is frequently used as a second-line treatment for patients who are not satisfied with the oral treatment. This review summarizes the use of and recent advances in intravesical therapy for IC/BPS.

2 DEFINITION AND EPIDEMIOLOGY OF IC/BPS

IC/BPS is a clinical diagnosis based on chronic pain perceived by the patient to derive from the bladder and/or pelvis associated with urinary urgency or frequency in the absence of other causes of the symptoms. The International Continence Society (ICS) prefers the term “painful bladder syndrome”, defined as “the complaint of supra-pubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and nighttime frequency, in the absence of proven urinary infection or other obvious pathology”. The American Urological Association (AUA) has adopted the Society for Urodynamics and Female Urology’s (SUFU) terminology of IC/BPS, along with the following definition: “an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes”. In the US, it was reported that, approximately 2.7%–6.5% of women aged ≥18 years (i.e. 3.3–7.9 million) met the criteria of IC/BPS. The RAND Interstitial Cystitis Epidemiology study found that the estimated prevalence of IC/BPS in men was 1.9%–4.2%.
the RAND study, most studies had reported a female-to-male preponderance of IC/BPS of 5:1 or greater, suggesting that this condition may be underdiagnosed and undertreated in the male population. Using the O'Leary-Sant symptom and problem index to select women with IC, Leppilahti et al. reported an estimated prevalence of IC/BPS was 300 per 100,000. Similar studies suggested an overall prevalence of IC/BPS was 306 per 100,000 in Austrian women and 265 per 100,000 in Japanese women. Using the Bristol Female Lower Urinary Tract Symptoms questionnaire, Song et al. reported that the prevalence of BPS symptoms for Fuzhou Chinese women was 98 per 100,000.

3 | DIAGNOSIS OF IC/BPS

The diagnosis of IC/BPS can be challenging and difficult for clinicians. Because patients present with a wide range of symptoms, physical examination findings, and clinical test results, they may be misdiagnosed or underdiagnosed, or diagnosis may be delayed. Symptom scores, such as the O'Leary-Sant symptom and problem index, may help assess patients and act as outcome measures. Rigid cystoscopy under a general anesthetic should be performed in patients with bladder pain. After excluding specific diseases, patients with symptoms according to the definition of AUA should be diagnosed with IC/BPS according to subtype and phenotype.

4 | CURRENT INTRAVESICAL THERAPY FOR IC/BPS

Treatment strategies for IC/BPS should start with more conservative therapies first, proceeding to less conservative therapies if symptom control is not adequate and/or the patient’s quality of life (QoL) is unacceptable. It has been suggested that appropriate manual physical therapy techniques be offered to patients who present with pelvic floor tenderness. Although oral medication, such as amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate, has been used to relieve the symptoms of IC/BPS in patients, the role of oral medication in IC/BPS is to support other forms of treatment.

Given that the pathogenesis of IC/BPS has been proposed as a wounded uroepithelium that induces a subsequent inflammatory reaction and sensory symptoms, it would be reasonable to assume that it would be best to apply medication directly in the bladder where it hurts. Intravesical instillation has been accepted as standard treatment for IC/BPS because it offers the following advantages: (i) a higher drug concentration in the bladder; (ii) reduced systemic side effects; (iii) reduced the drug–drug interactions caused by oral medications, which may affect efficacy; and (iv) directly repairs the urothelium defect.

However, intravesical drug delivery may be inadequate because of the impermeability of urothelial cells with tight junctions and umbrella cells on the apical surface, a short duration of action, and the need for frequent administration, which can be painful, costly, and associated with the risk of infection. Because of the multifactorial nature of the disease, multimodal treatment of IC/BPS through intravesical approaches acting through different mechanisms may improve therapeutic outcomes. Below, we review of literature describing the status of current and novel intravesical therapy for IC/BPS (Figure 1).

Several drugs and chemicals have been suggested to be effective for the treatment of IC/BPS, namely heparin, heparinoids such as hyaluronic acid, chondroitin sulfate, and PPS (Elmiron; Janssen, NJ), dimethylsulfoxide (DMSO), and botulinum onabotulinumtoxinA (BoNT-A). Table 1 summarizes results of intravesical therapy for IC/BPS in controlled and uncontrolled trials.

4.1 | Heparin

Weaver et al. first reported the use of intravesical therapy for the treatment of IC. Heparin has the ability to mimic the GAG lining of the bladder itself. It has anti-inflammatory effects and may also

![FIGURE 1](https://wileyonlinelibrary.com)
inhibit fibroblast proliferation, angiogenesis, and smooth muscle cell proliferation.\textsuperscript{38} In the bladder, there is little heparin is absorbed systemically, even in the inflamed bladder.\textsuperscript{39} Although uncontrolled studies have shown that subcutaneous heparin administration has some beneficial effects,\textsuperscript{40,41} the apparent risks of anticoagulation and osteoporosis have prevented this form of administration from further testing and general use. Currently, there is no agreement on the duration, frequency, or dose of intravesical heparin therapy. Endoscopic intravesical instillation with 10 000 units heparin in sterile water either individually or with DMSO at different intervals has been reported.\textsuperscript{42,43} Kuo treated 40 women with IC and a positive potassium chloride test with 25 000 units heparin twice weekly for TABLE 1 Summary of the effects of different treatments on pain reduction at 12 weeks and response rates in controlled and uncontrolled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Treatment</th>
<th>Total no. patients</th>
<th>No. instillations (12 weeks)</th>
<th>Pain (VAS) score Before treatment</th>
<th>Pain (VAS) score After treatment</th>
<th>Decrease in pain (VAS) score</th>
<th>Response rate (%)</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales et al.\textsuperscript{18}</td>
<td>1996</td>
<td>0.8% HMW-HA</td>
<td>25</td>
<td>6</td>
<td>6.7 ± 2.5</td>
<td>2.7 ± 3.7</td>
<td>4.00</td>
<td>71.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Riedl et al.\textsuperscript{19}</td>
<td>2008</td>
<td>0.8% HMW-HA (Cystitat, Mylan, CA, USA)</td>
<td>121</td>
<td>12</td>
<td>8.5 ± 1.7</td>
<td>3.5 ± 2.7</td>
<td>5.00</td>
<td>85.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Shao et al.\textsuperscript{20}</td>
<td>2010</td>
<td>Control</td>
<td>11</td>
<td>6</td>
<td>7.0 ± 1.0</td>
<td>6.6 ± 0.7</td>
<td>0.50</td>
<td>18.2</td>
<td>CT</td>
</tr>
<tr>
<td>Lai et al.\textsuperscript{21}</td>
<td>2013</td>
<td>0.8% HMW-HA (Cystitat, Mylan, CA, USA)</td>
<td>29</td>
<td>9</td>
<td>3.28 ± 2.45</td>
<td>2.13 ± 2.67</td>
<td>1.15</td>
<td>69.0</td>
<td>CT</td>
</tr>
<tr>
<td>Kallestrup et al.\textsuperscript{22}</td>
<td>2005</td>
<td>0.8% HMW-HA (Cystitat, Mylan, CA, USA)</td>
<td>20</td>
<td>6</td>
<td>4.7 ± 2.3</td>
<td>3.3 ± 3.0</td>
<td>1.40</td>
<td>65.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Gupta et al.\textsuperscript{23 a}</td>
<td>2005</td>
<td>0.8% HMW-HA (Cystitat, Mylan, CA, USA)</td>
<td>20</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>55.6</td>
<td>UCT</td>
</tr>
<tr>
<td>Engelhardt et al.\textsuperscript{24}</td>
<td>2011</td>
<td>0.8% HMW-HA (Cystitat, Mylan, CA, USA)</td>
<td>48</td>
<td>10</td>
<td>8.20 ± 1.70</td>
<td>2.71 ± 1.96</td>
<td>5.44</td>
<td>85.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Steinhoff et al.\textsuperscript{25 b}</td>
<td>2002</td>
<td>0.2% CS (Gepan instill; Pohl-Boskamp GmbH &amp; Co., UK)</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>92.3</td>
<td>UCT</td>
</tr>
<tr>
<td>Nickel et al.\textsuperscript{26}</td>
<td>2009</td>
<td>2% CS (Uracyst/Uropol S; Galen, UK)</td>
<td>53</td>
<td>10</td>
<td>6.9 ± 1.8</td>
<td>4.3 ± 2.3</td>
<td>2.60</td>
<td>60.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Nickel et al.\textsuperscript{27}</td>
<td>2012</td>
<td>Placebo</td>
<td>40</td>
<td>8</td>
<td>6.38 ± 1.83</td>
<td>4.66 ± 2.84</td>
<td>1.72</td>
<td>31.3</td>
<td>CT</td>
</tr>
<tr>
<td>Norling and van Ophoven\textsuperscript{28}</td>
<td>2008</td>
<td>0.2% CS (Gepan instill; Pohl-Boskamp GmbH &amp; Co., UK)</td>
<td>165</td>
<td>8</td>
<td>5.2 ± 2.6</td>
<td>3.3 ± 2.6</td>
<td>1.90</td>
<td>76.7</td>
<td>UCT</td>
</tr>
<tr>
<td>Porru et al.\textsuperscript{29}</td>
<td>2008</td>
<td>1.6% HA + 2% CS (iAluRil; Juno,AU)</td>
<td>23</td>
<td>12</td>
<td>5.4 ± 2.8</td>
<td>3.6 ± 2.5</td>
<td>1.80</td>
<td>46.0</td>
<td>UCT</td>
</tr>
<tr>
<td>Porru et al.\textsuperscript{30}</td>
<td>2012</td>
<td>1.6% HA + 2% CS (iAluRil; Juno,AU)</td>
<td>20</td>
<td>10</td>
<td>5.6 ± 2.3</td>
<td>3.2 ± 3.1</td>
<td>2.40</td>
<td>53.48</td>
<td>UCT</td>
</tr>
<tr>
<td>Bade et al.\textsuperscript{31}</td>
<td>1995</td>
<td>i-PPS 300 mg\textsuperscript{c}</td>
<td>6</td>
<td>24</td>
<td>7.5 ± 1.4</td>
<td>4.2 ± 2.3</td>
<td>3.33</td>
<td>66.7</td>
<td>UCT</td>
</tr>
<tr>
<td>Bade et al.\textsuperscript{32}</td>
<td>1997</td>
<td>Placebo</td>
<td>10</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.0</td>
<td>CT</td>
</tr>
<tr>
<td>Daha et al.\textsuperscript{33}</td>
<td>2008</td>
<td>i-PPS 300 mg\textsuperscript{c}</td>
<td>9</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Davis et al.\textsuperscript{34}</td>
<td>2008</td>
<td>i-PPS 200 mg\textsuperscript{d} + daily o-PPS 400 mg</td>
<td>20</td>
<td>36</td>
<td>4 ± 1</td>
<td>2 ± 2</td>
<td>2.00</td>
<td>85.7</td>
<td>UCT</td>
</tr>
<tr>
<td>Sairanen et al.\textsuperscript{35}</td>
<td>2009</td>
<td>DMSO</td>
<td>37</td>
<td>6</td>
<td>6.4 ± 2.21</td>
<td>-</td>
<td>-</td>
<td>30.0</td>
<td>CT</td>
</tr>
</tbody>
</table>
| BCG, intravesical Bacillus Calmette–Guérin; CS, chondroitin sulfate; CT, controlled trial; DMOS, dimethyl sulfoxide; HA, hyaluronic acid; HMW-HA, high molecular weight hyaluronic acid; i-PPS, intravesical pentosan polysulfate; o-PPS, oral pentosan polysulfate; UCT, uncontrolled trial.

Unless indicated otherwise, data are given as the mean ± SD.

Pain was assessed using a 10-point visual analog scale (VAS).

\textsuperscript{a} Results at 6 weeks.

\textsuperscript{b} Results at 24 weeks.

\textsuperscript{c} Intravesical instillation with 300 mg (3 capsules) Elmiron mixed with 50 mL of 0.9% sodium chloride.

\textsuperscript{d} Two hundred milligrams or 2 capsules mixed with 30 mL sterile normal buffered saline.
3 months. After treatment, 29 patients had a symptom score improvement of >50% and 8 patients had a symptom score improvement <50% but improved nocturia. Parsons also showed that intravesical treatment with the combination of 40,000 units heparin and alkalinized lidocaine (1% lidocaine [80 mg] or 2% lidocaine [160 mg] plus 3 mL of 8.4% sodium bicarbonate) immediately reduced the pain and urgency of IC in most patients treated for newly diagnosed IC.

4.2 | Hyaluronic acid

The GAG layer of the urothelium functions as an epithelial permeability barrier. When impaired, its functions can be duplicated by exogenous GAG. As a natural component of the GAG layer, hyaluronic acid (HA) was used to repair defects of the GAG layer of the urothelium. Morales et al. treated 25 patients with refractory IC with intravesical HA (40 mg weekly) for 4 weeks and then monthly for 6 months. In that study, there was an initial 56% positive response rate at Week 4, which increased to 71% by Week 12, with the response maintained until Week 20. Another study treated 121 patients with IC/BPS with monthly instillation of 50 mL phosphate-buffered saline solution containing 40 mg sodium hyaluronate for at least 10 weeks. Of 121 patients, 67 (55%) had no or minimal bladder symptoms after therapy. In all, 84% reported a significant improvement in their QoL, and this is the best outcome of intravesical HA therapy reported to date.

To compare the efficacy of intravesical instillation of HA and heparin, Shao et al. performed bladder hydrodistention followed by intravesical instillation of 40 mg HA weekly in the first month and then monthly in the following 2 months or instillation of 100 mg lidocaine with 12,500 U heparin, concluding that intravesical instillation of HA may significantly prolong the effects of bladder hydrodistention in patients with severe IC and that the effects of HA were better than those of heparin. Lv et al. treated 48 women with severe IC/PBS with intravesical 40 mg HA, 10 mL of 2% lidocaine, and 5 mL of 8.4% sodium bicarbonate on a weekly basis for 8 weeks, and then monthly for 4 months with a subsequent follow-up period of 24 weeks; the IC patients reported sustained relief of symptoms, with voiding frequency reduced by 67.25% and pain improved by 70.82%. Lai et al. compared the clinical effectiveness of different regimens of intravesical HA instillation for patients with IC/BPS. In their study, 30 patients were assigned to receive intravesical instillations once every week for 4 weeks with 40 mg HA followed by one instillation every month for 5 months (i.e., 9 doses of HA in 6 months), with another 30 patients receiving 12 intravesical instillations of 40 mg HA every 2 weeks (i.e., 12 doses of HA in 6 months). Both groups showed significant improvements in symptom scores and QoL. Lai et al. concluded that there was no significant difference in the therapeutic effect between the 2 HA instillation regimens. Generally, HA intravesical therapy has a good response rate, ranging from 69% to 93% (Table 1).

4.3 | Chondroitin sulfate

Chondroitin sulfate (CS) is also a component of the GAG layer. A deficit of CS proteoglycans in the bladder uroepithelium has been detected in IC/BPS patients. Like HA, CS has been used as in intravesical instillation therapy for PBS/IC patients. Different formulations of CS are available commercially for intravesical therapy, including iAluRil (Juno.AU) (CS 2.0%), Urcryst (Galen, UK) (CS 2.0%), and Uropol (Galen, UK) (CS 2.0%) and Gepan instill (Pohl-Boskamp GmbH & Co., UK) (CS 0.2%). Steinhoff et al. treated 18 IC patients with 40 mL of 0.2% CS intravesically once a week for 4 weeks and then once a month for 12 months, with a good response rate of 46.2% after the initial 3 months. Another multicenter community-based open-label study reported that instillation of 2% CS Urcryst/Uropol (Galen, UK) achieved a 60% response rate at 6 months. In the study of Nickel et al., a prospective randomized double-blind inactive vehicle-controlled study, women with IC/BPS were randomized to receive either 8 weekly bladder instillations of 20 mL of 2% CS or 20 mL inactive control solution. Of the 98 women enrolled in the study, 83% completed the study. More patients in the CS group (38.0%) reported moderate or marked improvement compared with the inactive control group (31.3%) at the 11-week endpoint visit. The authors concluded that intravesical CS therapy for IC/BPS may result in minor improvements in IC/BPS-related symptoms and pain. Nordling and van Ophoven used 0.2% CS (Gepan instill; Pohl-Boskamp GmbH & Co., UK) to treat 286 patients with clinically diagnosed chronic forms of cystitis, including PBS, IC, radiation cystitis, overactive bladder syndrome, and chronically recurring cystitis. The course of symptoms was documented over 8 instillations at maximum, covering a period of approximately 3 months. In that study, CS instillation was effective and well tolerated in the treatment of chronic forms of cystitis associated with a possible GAG layer deficit. Furthermore, Porru et al. demonstrated that the combination of HA and CS 2% (iAluRil; Juno.AU) is a safe and efficacious method of treatment for IC/BPS. It seems that the instillation of both HA and CS may provide better, longer-lasting therapeutic effects than HA or CS alone.

4.4 | Pentosan polysulfate

PPS, a heparin analog, has been shown to reinforce the GAGs and reduce urothelial injury. These observations underlie the rationale to use PPS for the treatment of IC, although different rates of success have been reported for oral PPS. For example, Bade et al. compared the efficacy of intravesical PPS treatment with placebo in 20 IC/BPS patients. Of these patients, 10 received intravesical PPS (300 mg in 50 mL of 0.9% sodium chloride) administered twice a week for 3 months, whereas the other 10 received placebo. There was a significant increase in urodynamic bladder capacity in patients treated with PPS. Bade et al. suggested that intravesical PPS is an effective option for the treatment of IC/BPS. In another prospective uncontrolled open-label study, 29 female patients with IC/BPS received 300 mg PPS intravesically twice a week for 10 weeks and thereafter voluntary maintenance therapy once a month for 3 months, with 25 patients completing the 10-week treatment and the 3-month follow-up. In that study, intravesical treatment with PPS reduced both the pain score by visual analog scale (VAS) and the O’Leary-Sant symptom and problem index in patients with IC/BPS. In another study, Davis et al. examined the safety and efficacy of a combination
of intravesical and oral PPS compared with oral only PPS in treating IC/BPS. A total of 41 women diagnosed with IC/BPS were treated with combination therapy or oral PPS alone for 6 weeks, with all subjects continuing to receive oral PPS for another 12 weeks. At Week 18, the combination treatment group showed a significant improvement in all health-related QoL domains compared with the baseline. The authors of that study concluded that intravesical PPS simultaneously with oral PPS is a safe and effective therapeutic option. Based on these studies, it appears that the combination of intravesical and oral PPS has a higher response rate than intravesical PPS alone.

4.5 | Dimethylsulfoxide

The mechanism underlying the effects of DMSO in relieving the symptoms of IC/BPS is assumed to be a combination of anti-inflammatory effects, nerve blockade, smooth muscle relaxation, and collagen inhibition. In clinical use, DMSO can be instilled weekly, with 50 mL of 50% w/w DMSO administered via bladder catheter for 6 weeks. The AUA guideline panel suggests limiting the dwell time to 15–20 min due to the severe pain associated with rapid DMSO absorption by the bladder wall. Three randomized control trials (RCTs) have investigated DMSO therapy for IC/BPS. Perez-Marrero et al. reported that 53% of DMSO-treated IC/BPS patients exhibited marked improvement, compared with 18% of placebo-treated patients. Of the DMSO group, 93% had objective improvement compared with 35% in the placebo group. The other 2 RCTs investigated outcomes of DMSO versus those with Bacillus Calmette–Guérin (BCG) in the treatment of IC/BPS, finding that, overall, intravesical DMSO appeared to be more effective than BCG. Five clinical studies have investigated the efficacy of DMSO therapy in combination with heparin, hydrocortisone, triamcinolone, and/or local anesthetic, known as “cocktail” preparations, with response rates ranging from 61% to 70% over up to 13 months of follow-up. However, the efficacy in these studies did not exceed the outcomes seen with DMSO alone, indicating that there was no benefit with the “cocktail” therapy.

Treatment relapse after a series of DMSO instillations is common. For patients who initially respond to DMSO therapy, a repeat series of 6 instillations may be necessary. Other therapies, such as intravesical lidocaine, intravesical heparin, or more invasive therapies, can be tried if patients fail to respond to repeated doses of DMSO.

4.6 | Botulinum onabotulinumtoxinA

BoNT-A is widely used in clinical practice. The action of BoNT-A starts with its internalization following binding to its ~100-kDa heavy chain to a specific receptor on the membrane of presynaptic neurons in cholinergic nerve terminals. BoNT-A is then engulfed into endocytic vesicle, where it undergoes a pH-dependent conformational change, leading to the translocation of its ~50-kDa light chain into the cytosol. After entering the cytosol, the light chain cleaves synaptosome associated protein 25 (SNAP-25), part of the soluble N-ethylmaleimide-sensitive fusion attaches to protein receptor (SNARE) complex, which mediates the fusion of the acetylcholine-containing vesicles with the presynaptic membrane. This interaction eventually interrupts the release of neurotransmitter into the synapse, resulting in flaccid paralysis of the muscle. It also inhibits the release of neurotransmitters from the urothelium. In addition, intradetrusor injections of BoNT-A have been reported to decrease the sensory purinergic P2X3 and transient receptor potential vanilloid 1 (TRPV1) receptors in suburothelial nerve fibers and to reduce nerve growth factor (NGF) content, associated with decreases in OAB symptoms in patients with detrusor overactivity. Intravesical BoNT-A injections have been used to treat IC/BPS since 2004. Smith et al. reported that of 13 patients receiving 200 IU BoNT-A trigonal and bladder base injections, 9 (69%) reported subjective improvement after BoNT-A treatment. In another study, Pinto et al. injected 100 U BoNT-A in 10 trigonal sites (10 U per 1 mL saline) in 26 women with IC/BPS, with all patients reporting subjective improvements at the 1- and 3-month follow-ups. Pain, daytime, and nighttime voiding frequency, Overactive bladder symptom score (OABSS), and QoL improved significantly, and bladder volume to first pain and maximal cystometric capacity more than doubled. Treatment remained effective in >50% of patients for 9 months. Recently, a multicenter randomized double-blind placebo-controlled trial in patients with IC/BPS refractory to conventional treatment was conducted in Taiwan. In all, 60 patients (8 males, 52 females; age 50.8 ± 13.9 years) were enrolled, 40 receiving BoNT-A treatment and 20 receiving normal saline. Patients in the BoNT-A group received hydrodistention plus intravesical suburothelial injections of 100 U BoNT-A. Pain was assessed using a VAS at Week 8 after treatment, with the overall success rate higher significantly in the BoNT-A compared with normal saline group (63% vs 15%, respectively; P = .029). Giannantoni et al. treated 3 men and 12 women with IC/BPS by injected 200 U botulinum A toxin diluted in 20 mL of 0.9% NaCl submucosally in the bladder trigone and lateral walls. Overall, 13 patients (86.7%) reported subjective improvement at the 1 and 3-month follow-up visits; however, the beneficial effects decreased progressively within a few months. At the 12-month follow-up, pain had recurred in all patients. Giannantoni et al. concluded that repeat injections of the neurotoxin are required for efficacious treatment in patients with the disease.

BoNT-A has been designated as the fourth-line treatment for IC/BPS by the AUA IC/BPS Guideline Panel. The panelists suggested a major shift in how BoNT-A is administered to treat IC/BPS in several ways, including combination of BoNT-A with hydrotension, the use primarily of the 100-U dose, the use of repeat treatments with symptom return, and following-up patients for years rather than months. A very recent meta-analysis showed that BoNT-A therapy has the highest probability of being the best therapy according to global response assessment, and significantly improves bladder capacity in IC/BPS patients.

5 | POSSIBLE INTRAVESICAL TREATMENT FOR IC/BPS IN THE FUTURE

5.1 | Liposomes

Liposomes (LPs) are spherical vesicles composed of concentric phospholipid bilayers enclosing an aqueous interior. LP have been used as vehicles for the delivery of genes and pharmaceutical drugs. Furthermore, intravesically administered LPs have been shown to reduce...
bladder hyperactivity induced by protamine sulfate and KCl or acetic acid in a rat model.\(^72\) LPs may use surface ligands to attach to the injured uroepithelium and assist in the repair of leaky inflamed uroepithelium.\(^72,73\)

Chuang et al.\(^74\) reported on the findings of an open-label study comparing the effects of intravesical LP-08 (Lipella, Pittsburgh, PA, USA); 80 mg/40 mL distilled water, once weekly for 4 weeks against those of oral PPS (100 mg thrice daily for 4 weeks) in 24 patients with IC/BPS patients. Both LPs and oral PPS significantly decreased urinary frequency and nocturia, indicating a comparable efficacy of LP. Urgency was significantly reduced in the LP group, accompanied by significant decreases in pain and the O'Leary-Sant symptom and problem index.\(^74\) In another study performed in 17 IC/BPS patients treated with 4-weekly LP instillation (Group 1; \(n = 12\)) or twice weekly instillations for 4 weeks (Group 2; \(n = 5\)), the O'Leary-Sant symptom and problem index total and pain scores were significantly better without any unanticipated adverse events in Group 2 than in Group 1.\(^75\) These results suggest that a higher frequency of administration of LPs may have better outcomes in severely inflamed bladder. The therapeutic effects of LPs in IC/BPS patients were further confirmed by Peters et al.\(^76\) in 14 patients with IC/BPS treated with intravesical LP once a week for 4 weeks in an open-label study. Future large-scale placebo-controlled studies are needed to confirm the true value of LPs in the treatment of IC/BPS.

5.2 | Liposomal-mediated BoNT-A

As a neurotoxin with a high molecular mass (150 kDa), BoNT-A cannot pass the urothelial barrier to the submucosal nerve plexus and must be injected directly into the submucosal layer. However, intravesical injections may be associated with adverse events, such as urinary tract infection, urinary retention, pain, and hematuria. Furthermore, anesthesia during the procedure makes it inconvenient and risky for patients. Transportation of BoNT-A into the urothelium via LPs has been proposed based on their carrier potential, characteristics of adsorption, and the ability to fuse with the cell membrane.

The unique effects of liposome-mediated BoNT-A (Lipo-BoNT-A) on neurotransmitters and proteolysis of SNAP-25 have been confirmed by western blotting analysis and immunohistochemistry.\(^77\) A double-blind randomized parallel controlled pilot trial was conducted in 24 OAB patients, with intravesical instillation of Lipo-BoNT-A containing 80 mg LPs and 200 U BoNT-A or normal saline.\(^78\) In that study, intravesical Lipo-BoNT-A instillation effectively reduced frequency episodes 1 month after treatment, without any increase in post-voiding residual urine or risk of urinary tract infections. In addition, expression of Synaptic vesicle glycoprotein 2A (SV2A) and SNAP-25 in urothelial cells and suburothelial tissues was demonstrated, raising the possibility that Lipo-BoNT-A may have effects on the urothelium.\(^78\) Chuang and Kuo recently completed a 2-center double-blind randomized placebo controlled physician-initiated study enrolling patients with refractory IC/BPS.\(^79\) That study failed to demonstrate positive proof of concept for Lipo-BoNT-A compared with BoNT-A or placebo. However, a single intravesical instillation of Lipo-BoNT-A was associated with decreased IC/BPS symptoms compared with baseline in patients with moderate to severe IC/BPS; this effect was though to be a significant placebo effect.\(^79\) Further clinical trials with different protocols are needed to confirm the efficacy of Lipo-BoNT-A in treating IC/BPS.

5.3 | Liposomal tacrolimus

Tacrolimus may have local anti-inflammatory effects because of its potent immunosuppressive effects. LPs formulated with tacrolimus were recently tested as a potential treatment for IC/BPS.\(^80\) with single-dose application significantly reducing the inflammation and voiding changes associated with chemotherapy-induced hemorrhagic cystitis in rats. Successful delivery of tacrolimus in the bladder also decreased expression of the prostanoid EP\(_4\) receptor in the urothelium, and infiltration of inflammatory cells in the suburothelial region.\(^80\) Increased bladder tissue and urine concentrations of prostaglandin E\(_2\) and interleukin (IL)-2 are also reduced by liposomal tacrolimus,\(^80\) and liposomal tacrolimus has been shown to reduce inflammation and improve voiding outcomes in a rat model of radiation cystitis.\(^81\) However, clinical trials are needed before liposomal tacrolimus can be used for the treatment of human IC/BPS.

5.4 | Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF)-driven processes in bladder urothelial cells and ganglia during the course of inflammation have been established.\(^82\) Cheppudira et al.\(^83\) also demonstrated that urinary bladder inflammation and NFG regulate the VEGF receptor system in the urinary bladder. Bladder instillation of a targeted fluorescent tracer, an engineered single-chain VEGF labeled with Cy5.5 dye (scVEGF/Cy), showed preferential accumulation at sites of bladder inflammation and in ganglia.\(^84\) Therefore, increased angiogenesis at sites of inflammation and ulcers in IC/PBS can be targeted with ligands for the VEGF receptor.\(^82\)

5.5 | Continuous intravesical lidocaine

According to the latest European Association of Urology (EAU) guidelines for chronic pelvic pain,\(^85\) lidocaine could to treat IC/BPS in combination with heparin and sodium bicarbonate. There are sporadic reports of successful treatment of BPS with intravesical lidocaine.\(^88\) Alkalization of lidocaine improves its pharmacokinetics. Intravesical instillation of alkalized lidocaine or placebo for 5 consecutive days resulted in significantly sustained symptom relief for up to 1 month.\(^88\) Using elastomeric polymers, a continuous lidocaine-releasing intravesical system (LiRIS) was designed to be retained in the bladder through cystoscopy and to release therapeutic amounts of the drug into the urine over a period of 2 weeks.\(^86\) In the LiRIS, lidocaine is contained in powdered form instead of in solution. Nickel et al.\(^86\) reported on 16 women with IC/BPS who met the National Institute of Diabetes and Digestive and Kidney Diseases criteria for bladder hemorrhage or Hunner’s lesions and were treated with either 200 or 650 mg LiRIS for 2 weeks. Clinically meaningful reductions in pain, urgency, voiding frequency, and disease questionnaires were seen. Cystoscopic examinations showed improvement on Day 14 (the day of removal) compared with Day 1, including resolution of Hunner’s lesions in 5 out of 6.\(^86\) Global response assessment showed an overall responder rate of 64% on Day 14. At the
2-week post-removal visit, 63% (5/8) of subjects who had received 200 mg LIRIS and 67% (4/6) of those who had received 650 mg LIRIS reported moderate or marked improvement in symptoms compared with baseline.\textsuperscript{66} Extended follow-up suggested that the reduction in pain was maintained for several months after the device was removed. Both doses were well tolerated. The unexpected longer duration of effects and healing of ulcers could be due to the anti-inflammatory actions of lidocaine over the 14-day treatment period.

6 | CONCLUSION

IC/BPS is a complicated condition caused by multiple etiologies and pathological pathways. It is still a pathophysiological enigma and considered a multifactorial process that ends with an imbalance in the damage repair process in the urothelium, leading to a deficiency of the GAG layer and subsequent symptoms. From abnormal urothelial permeability, sensory nerve stimulation, and to mast cell activation, this complex process contributes to the severity and unsatisfactory responses of IC/BPS to treatment. Despite extensive empirical use of intravesical agents, the evidence for efficacy is the early phases. Although some intravesical agents, such as GAG analogs and DMSO, have shown promise in relieving symptoms of IC/BPS (Table 1), there remains a lack of large RCTs and clinical research in this field. The LP platform has certainly improved clinical outcomes in IC/BPS and OAB patients. Various drugs discussed herein may become new treatments in intravesical therapy of IC/BPS in the future.

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