

Review of intravesical therapies for bladder pain syndrome/interstitial cystitis

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Abstract: Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic pain condition characterised by urinary frequency, urgency and pain or discomfort which the patient attributes to the bladder. It is a complex condition to manage and treat and requires a multi-disciplinary and multi-modal approach. As well as lifestyle and behavioural modifications, physical therapy and oral medications, intravesical treatments can be used in the treatment algorithm for BPS/IC. A number of intravesical agents are reviewed in this paper along with the available evidence for their use.

Keywords: Bladder pain syndrome (BPS); interstitial cystitis (IC); intravesical therapy; instillation therapy

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Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic pain syndrome characterised by pain/discomfort attributed to the bladder, with associated urgency and urinary frequency. According to the American Urological Association (AUA) guidelines, symptoms should be present for a period of more than 6 weeks (1). Confusable diseases, such as overactive bladder and recurrent urinary tract infection, need to be excluded prior to a diagnosis of BPS/IC.

The underlying etiology of BPS/IC is not well understood and it is likely that a number of mechanisms play a role in the development of the condition. The urothelium/transitional epithelium is thought to play a fundamental role in the pathogenesis of BPS/IC. The protective layer of glycosaminoglycans (GAG) on the surface of the urothelial cells provides a barrier against solutes in the urine. Components of this layer include hyaluronic acid (HA), chondroitin sulfate (CS), heparin sulfate, dermatan sulfate and keratin sulfate (2). This GAG layer has been shown to be defective in some patients with BPS/IC (3-5).

Once the subepithelial cells come into contact with urinary solutes, an inflammatory reaction is triggered, in turn resulting in decreased urothelial production of GAG and exacerbation of urothelial permeability and inflammation. Urothelial damage results in pathologic C-fiber activation, causing smooth muscle contraction, neurogenic inflammation, and hypersensitivity. As with other chronic pain conditions, central pain sensitisation results.

Management of BPS/IC requires a multimodal approach. The AUA and the European Urological Association have produced management guidelines for BPS/IC, both of which were updated in 2014 (6,7).

First line therapy is aimed at educating the patient about the chronic nature of the condition and advocating behavioural and lifestyle modifications that may help ameliorate the symptoms, as well as providing a pain management plan.

Intravesical therapies are indicated if first line therapy fails and are used in conjunction with physiotherapy techniques (myofascial release/pelvic floor muscle relaxation) and oral agents. The rationale for the use of

many of the currently used intravesical therapies is to replenish the deficient GAG layer or to alter the process of neurogenic inflammation and hypersensitivity.

Intravesical therapy has the advantages of localising therapy to the bladder, with the establishment of high concentrations of the agent and minimising systemic side effects. The disadvantages are that delivery of the agent requires instrumentation of the urethra and bladder with the potential for exacerbating pain and increasing the risk of urinary tract infection.

This review of intravesical therapies for the treatment of BPS/IC summarises the rationale and evidence for the use of these agents. A PubMed search was performed using the terms “bladder pain syndrome”, “interstitial cystitis”, “intravesical”, “instillation” along with the names of the individual agents, with publication dates up to June 2015. Reference lists of reviewed articles were also searched for additional papers.

Intravesical therapies

Dimethyl sulfoxide (DMSO)

Mechanism of action

DMSO is an organosulfur non-toxic solvent used in the treatment of BPS/IC since the 1970's when it was approved by the US Food and Drug Administration (FDA) for intravesical use. It is likely to exert its clinical effect through several mechanisms: reducing inflammation, acting as an analgesic and facilitating detrusor relaxation (8,9). It can be given as a single-agent instillation at a 50% concentration or, more commonly, as part of a ‘cocktail’ with methylprednisolone or hydrocortisone, alkalised lidocaine and heparin sulfate. Instillation regimens differ but a common treatment program involves twice weekly instillations for 4 weeks and then weekly instillations for a further 4 weeks, for a total of 12 instillations. Repeat full, partial (four weekly instillations) or maintenance (monthly) treatment courses for persistent or recurrent symptoms are possible.

Evidence

Both the AUA and EAU guidelines list DMSO as one of the instillation agents of choice. This is largely based on a few small case series published in the 1970's and 80's with variable follow-up and using non-standardised outcome measures. Response rates in these studies range from 70-95% (10-13).

Perez-Marrero *et al.* performed a randomised, placebo-controlled crossover trial in 33 patients and assessment was based on urodynamics and symptoms (14). Compared to placebo, DMSO showed higher objective (35% *vs.* 93%) and subjective (18% *vs.* 53%) improvement. Peeker *et al.* performed a randomised, double-blind crossover study comparing DMSO to intravesical BCG in 21 patients (15). Each group underwent six weekly instillations and crossed-over to the other treatment if no improvement was noted. Patients were assessed with symptom questionnaires, VAS pain scale and voiding diaries. No improvement in any of the outcome measures were seen following BCG (but the study was likely to be underpowered). DMSO resulted in significant reductions in pain and urinary frequency.

Ghoniem *et al.* utilised a DMSO cocktail (premixed 50 mL solution of 50% DMSO, 40 mg methylprednisolone and 5,000 units of heparin sulfate) in a case series of 25 patients. Six instillations (the first performed under general anaesthesia after hydrodistention) were administered at weekly intervals. Outcome measures were not well defined, with 92% achieving initial remission for an average of 8 months. Nine patients (36%) had one or more relapses and required further instillations or oral therapy.

Lim *et al.* reported long-term outcomes following DMSO cocktail instillation (50 mL of 50% DMSO, 100 mg hydrocortisone, 0.25% bupivacaine and 5,000 units heparin) (16). Mean follow-up of 55 patients was at 4.65 years and overall improvement as assessed on ICSI/ICPI and VAS pain scores was 23-47%. At long-term follow-up 34% were cured after one course, a further 22% required oral medication, 24% had a DMSO top-up; the remainder went on to receive other treatments. Anaesthetic bladder capacity \leq 500 mL was associated with a lower response rate.

Heparin and lidocaine

Mechanism of action

Heparin is a sulfonated GAG with the theoretical action of replenishing the urothelial GAG layer. Heparin also acts as an anti-inflammatory, inhibits fibroblast proliferation and promotes angiogenesis and smooth muscle cell proliferation (17). Lidocaine is a topical anaesthetic and is used as a single-agent instillation or, more commonly, in combination with heparin. It is given in a variety of formulations and concentrations and usually in combination with an alkalisng agent (sodium bicarbonate) to avoid ionisation within urine and to better penetrate the urothelium (18).

Evidence

Single-agent heparin studies have shown modest benefit in patients with BPS/IC. Parsons *et al.* reported on 48 patients undergoing instillation with 10,000 units of heparin 3 times a week for 3 months. Fifty-six percent attained “good clinical remission” (19).

Single-agent alkalised lidocaine (200 mg lidocaine plus 8.4% sodium bicarbonate, 10 mL) was reported by Nickel *et al.* in a randomised, double-blind placebo-controlled industry sponsored study of 102 patients (18). Instillations occurred daily for 5 consecutive days. The primary outcome was based on a Global Response Assessment. On day 8, patients in the lidocaine group had significantly higher improvement than placebo (30% *vs.* 10%, $P=0.012$); this improvement was still present at day 15 but not statistically significant (24% *vs.* 12%, $P=0.102$). Eighty-two patients elected to continue on to the open-label phase of the study and underwent a further 5-day course of lidocaine with similar rates of improvement.

In an effort to improve response rates, multi-agent therapy with heparin and alkalised lidocaine has been studied. Parsons *et al.* have studied the efficacy of heparin and alkalised lidocaine in a total of 82 patients (20). Group 1 received 40,000 units heparin, 8 mL of 1% lidocaine and 3 mL of 8.4% sodium bicarbonate. Group 2 received an increased concentration of lidocaine (8 mL of 2% lidocaine). Immediate relief of pain and frequency after 1 instillation was higher in group 2 than group 1 (94% *vs.* 75%; $P<0.01$). Twenty patients in group 2 underwent a further 6 instillations over 2 weeks, 80% showed symptom relief persisting at least 48 hours after the last treatment. Improved duration of effect was shown by Nomiya *et al.* in a study of 32 patients undergoing 12 weekly instillations of 20,000 units heparin, 5 mL 4% lidocaine and 25 mL 7% sodium bicarbonate. On GRA, 76% responded at the end of treatment, with responses of 90% at 1 month, 46% at 2 months and 16% at 6 months following treatment (21).

Pentosan polysulfate sodium (PPS)

Mechanism of action

PPS is the only oral agent approved for BPS/IC by the FDA. It is an oral heparinoid and likely exerts its effect in the treatment of BPS/IC by restoring the GAG layer. It also inhibits histamine release by mast cells and reduces the intracellular calcium ion levels in the bladder (22). The main disadvantage is the low urine concentrations achieved, resulting in a lag time of up to 6 months before clinical

improvement is observed. Intravesical therapy has the theoretical advantage of achieving a more rapid response to PPS treatment.

Evidence

Davis *et al.* performed a randomised, double-blind controlled study comparing oral PPS and intravesical PPS to oral PPS and intravesical placebo in 41 patients (23). Instillations occurred twice weekly for 6 weeks whilst oral therapy was given for a total of 18 weeks. At the end of the study period, the treatment group were shown to have a statistically greater reduction in ICSI/ICPI scores compared to placebo (46% reduction *vs.* 24% reduction; $P=0.04$). Health-related quality of life domains also showed statistically greater improvement in the treatment group.

Sodium hyaluronate (HA)

Mechanism of action

The rationale for using HA is to replenish deficiencies in the GAG layer although other biological activities including enhancement of connective tissue healing and inhibition of leukocyte migration and aggregation may contribute to its action in BPS/IC patients. HA is commercially available as Cystistat (Teva UK Limited); it comes as a 40 mg dose in a 50 mL solution. Most studies use a treatment regimen consisting of four weekly instillations followed by monthly therapy until symptoms have resolved.

Evidence

Riedl *et al.* prospectively studied the efficacy of HA in 126 patients as first line therapy. Weekly instillations of HA were given until patients were significantly improved or symptom free. Assessment was based on a non-standardised questionnaire using a VAS symptom score, impact on quality of life question and willingness to undergo repeat instillation therapy. This was administered at baseline and at a mean of 6 months after the last HA instillation. The average number of instillations was 12.2. Eighty-five percent of patients reported symptom improvement (≥ 2 VAS units); 55% had no or minimal bladder symptoms after therapy. Eighty-four percent reported improved quality of life (although this was not objectively quantified) and 86% would undergo repeat HA treatment if necessary. Thirty-four percent had recurrence of symptoms and required further instillations—the duration of effect before restarting treatment was not stated. The same group then published long-term follow-up data of 48/70 patients from

this cohort who were contacted at a mean follow-up of 5 years (24). Fifty percent (24/48) had sustained improvement and did not require any further treatment. Forty-one percent continued with intermittent HA instillation therapy with or without oral pentosan polysulfate.

A number of smaller case series have reported improvement rates with HA instillation of between 30-85% with varying follow-up times and instruments used to assess outcomes (25-29).

Shao *et al.* performed a prospective open-label controlled trial in 47 patients examining the use of HA after hydrodistention (30). Patients with functional bladder capacities <200 mL underwent hydrodistention followed by treatment with either HA (n=20) or a heparin/lidocaine cocktail (n=16). Treatments occurred weekly for 4 weeks, then monthly for a further 2 months. Eleven patients served as 'controls' undergoing only hydrodistention. Assessment was based on urinary frequency, bladder capacity, and VAS pain score at baseline and 3, 6 and 9 months following hydrodistention. At 6 months, 78% in the HA group and 33% in the heparin group had improvement in their symptoms versus 9% in the hydrodistention group. At 9 months, improvement was sustained (but diminished) in the HA group but not in the heparin group. There were no adverse effects related to HA or heparin however two patients had bladder rupture during hydrodistention.

Gulpinar *et al.* reported on the use of electromotive drug administration (EMDA) to improve the efficacy of HA treatment (31). EMDA increases tissue uptake of drug compared with passive diffusion. Thirty-one patients were randomised to instillation of HA alone (n=15) or HA with EMDA with placement of suprapubic electrodes (n=16). Patients were not blinded to treatment allocation. Follow-up was at 1, 6, 12 and 24 months. Both groups had statistically significant improvement in all parameters assessed (urinary frequency, nocturia, VAS pain, voided volume, ICSI/ICPI and global response assessment) at 6 and 12 months; the percentage of responders was higher in the EMDA group than in the HA alone group (69% *vs.* 58%, $P=0.042$). By 24 months, only voiding frequency and VAS pain scores were still significantly improved from baseline in both groups.

Two industry-sponsored (Bioniche Life Sciences and Seikagaku Corporation) randomised, placebo-controlled trials of HA were completed in 2003/2004 (32). Both trials showed non-significant improvements in the treatment group compared to placebo and remain unpublished in the peer-reviewed literature.

Chondroitin sulfate (CS)

Mechanism of action

CS is a component of the GAG layer and has been shown to be deficient in patients with BPS/IC (33). As well as its role in the GAG layer, CS has been shown to inhibit the recruitment of inflammatory cells to the deep layers of the bladder wall (34).

Evidence

Nordling *et al.* conducted a multi-centre, prospective observational trial of 40 mL of 0.2% CS (Gepan[®] Instill, Pohl-Boskamp GmbH, Hohenlockstedt, Germany) in 286 patients with chronic cystitis (51% were BPS/IC patients) (35). Instillations occurred weekly for the first 4-6 weeks, then monthly until 12 weeks with a maximum of 8 instillations. Outcome measures from baseline to end of study included change in daytime and nocturnal frequency, urgency and pain scores and a global response assessment. Overall, statistically significant changes were seen in all parameters and this was also seen in a subgroup analysis of the BPS/IC patients. GRA response was 76%.

Nickel *et al.* conducted a similar multi-centre, prospective observational study of 20 mL 2% CS (Uracyst[®], Stellar Pharmaceuticals Inc., London, ON, Canada) (36). Fifty-three patients underwent 6 weekly instillations followed by a further four instillations at monthly intervals. Global response was assessed at week 10 and 24 with rates of 47% and 60%, respectively. At week 24, ICSI and ICPI scores significantly decreased as did VAS pain and urgency scores.

More recently, Nickel *et al.* conducted a randomised, double-blind, inactive vehicle control trial of 20 mL 2% CS (Uracyst[®], Stellar Pharmaceuticals Inc., London, ON, Canada) (37). Ninety-eight patients underwent eight weekly instillations, then monthly treatments to a maximum of 10. No statistically significant results were obtained with respect to GRA (treatment group 38% *vs.* control 31%) or based on changes in ICSI/ICPI scores, frequency, urgency, voided volume or VAS pain scores. The authors noted that the study was underpowered and based on these results would require a total of 1,500 patients to be adequately powered to show a difference in outcomes between the two groups, however the author's conclusion was that single-agent therapy with CS could not be supported.

Sodium hyaluronate and chondroitin sulfate (HA-CS)

Mechanism of action

HA-CS has been shown to reduce the production of

proinflammatory cytokines, reduce urothelial permeability, and facilitate the repair of the protective GAG layer (38). HA-CS is available as a 50 mL proprietary preparation (Ialuril®; IBSA Institut Biochimique SA, Lugano, Switzerland) containing 1.6% HA and 2% CS with calcium chloride in water.

Evidence

To date, three small case series with a total of 63 patients have been published assessing treatment response to HA-CS (39-41). Instillations occurred weekly for a period of 4-20 weeks, with further biweekly or monthly instillations until treatment response was assessed. All studies reported significant changes from baseline in ICSI/ICPI scores. Cervigni and Porru showed significant changes from baseline in VAS pain and urgency scores.

Cervigni *et al.* presented at ICS 2014 an IBSA funded study comparing 13 weekly instillations of Ialuril with DMSO in a 2:1 random allocation with 110 subjects with ESSIC criteria for BPS (42). The baseline demographics and VAS pain scores were similar. The results were a VAS score reduction of -39 (SD 25) *vs.* -31 (SD 26) points for ialuril and DMSO respectively. Response at 6 months defined as >30% reduction of the VAS from baseline was 73% *vs.* 58% for ialuril and DMSO respectively. Adverse events were higher in the DMSO group at 31% *vs.* 15%. There were seven dropouts overall and were evenly divided.

Oxychlorosene sodium (OS)

Mechanism of action

OS is a stabilised organic derivative of hypochlorous acid. It has been used as an antibacterial agent extensively in general surgery, particularly in the irrigation of wounds. It is available as a proprietary preparation under the name of Clorpactin® (Guardian Laboratories, United-Guardian Inc, Hauppauge, New York, USA). Its use in the BPS/IC population stemmed from its role in tuberculous cystitis, when infection was thought to be an inciting event in the BPS/IC cascade. The exact mechanism of action of OS in BPS/IC is unclear but some have hypothesised that it may act by desensitising or degranulating bladder nociceptive nerve endings (43).

Evidence

Initial case series published in the 1950's and 1970's provided some encouraging results, with response rates of 70-80%. OS has been designated as a historical treatment

in a number of reviews of intravesical therapy for BPS/IC. The authors are currently involved in a multi-centre, randomised, single-blind controlled trial assessing the efficacy of a single instillation of 0.4% OS under general anaesthesia compared to hydrodistension (Australian New Zealand Clinical Trials Registry: 12611000717954).

Botulinum toxin A

Mechanism of action

Botulinum toxin A is a potent neurotoxin. It has been shown to inhibit the release of acetylcholine and other neurotransmitters from both afferent and efferent nerve terminals as well as ATP from the urothelium (44). Chronic inflammation and apoptotic signalling molecules is significantly reduced following intravesical botulinum toxin A injections, but only after repeated injections (45). The recently amended AUA guidelines for the treatment of BPS/IC have moved botulinum toxin A from 5th to first 4th line treatment (1).

Evidence

Most studies of botulinum toxin A use onabotulinum toxin A (Botox®, Allergan, Irvine, CA, USA). A number of case series with between 11-16 patients each, showed that intravesical injections of 100-200 units of Botox resulted in high response rates of 71-100% (46-49). Significant reductions in VAS pain scores, urinary daytime and night-time frequency were seen at 3 months follow-up. These studies varied in the dose injected, the number of injections and the site of injection (trigonal *vs.* supratrigonal).

Kuo *et al.* performed a multi-centre, randomised, double-blind placebo-controlled trial of Botox in BPS/IC patients refractory to conventional treatment (50). Forty patients underwent suburothelial injections of 100 units Botox and hydrodistension whilst 20 control patients underwent normal saline injections and hydrodistension. At 8 weeks post-treatment, overall success was greater in the Botox group compared to the control group (63% *vs.* 15%, $P=0.028$). VAS pain scores (-2.6 *vs.* -0.9, $P=0.021$) and cystometric capacity (+67.8 *vs.* -45.4, $P=0.02$) were also significantly changed in the Botox group compared to placebo. Adverse events including dysuria (16/40 Botox, 1/20 control), urinary tract infection (2 Botox), urinary retention (1 Botox) and haematuria (1 Botox) were all greater in the Botox group. In a prospective case series of 44 patients undergoing 6 monthly Botox injections, Lee and Kuo reported that Botox was not beneficial in ulcer type

BPS/IC patients (51).

Manning *et al.* reported on the use of abobotulinumtoxin A (Dysport[®], Ipsen Biopharmaceuticals Inc., Basking Ridge, NJ, USA) (52). This was a multi-centre, randomised, double-blind placebo-controlled trial in 54 patients. Dysport 500 U suburothelial injections plus hydrodistension was compared to normal saline injections plus hydrodistension. O'Leary Sant overall scores were improved in both groups at 3 months with no statistically significant difference seen between the two groups. Only the OLS-problem index improved in the Dysport group (P=0.04). Interestingly, this study found that post-treatment UTI was a confounder and that when the 12 patients were excluded from the analysis, the OLS overall score and OLS-symptom index were significantly improved in the Dysport group. The authors concluded that Dysport may be beneficial in a small number of patients and that patients without post-treatment UTI had a better response.

Other intravesical therapies

Capsaicin and resiniferatoxin are C-fiber afferent neurotoxins. They have been considered as candidates for treatment of BPS/IC based on their theoretical ability to alleviate bladder symptoms by desensitising bladder afferents (53). Whilst clinical efficacy for resiniferatoxin was initially demonstrated in a number of small studies (54-57), these results have not been confirmed in placebo-controlled studies (58,59). They are currently not recommended for intravesical use in BPS/IC patients.

Bacillus Calmette-Guerin (BCG) is an immunomodulatory agent used for the intravesical treatment of bladder cancer. An initial open label study provided promising results (60), however a randomised double blind study demonstrated no clinical benefit (61,62). Adverse events may be serious and therefore BCG is not recommended for use in BPS/IC patients.

Liposomes are phospholipid vesicles and when applied to cell walls they create a molecular film. It is believed that they may be able to restore the GAG layer. A small pilot study has shown significant improvement in frequency, nocturia, and pain in 24 patients undergoing intravesical liposomal instillations compared to oral PPS (63). A randomised, placebo-controlled trial is currently underway assessing the efficacy of two doses of intravesical liposomal therapy compared to placebo (<https://clinicaltrials.gov/show/NCT01393223>. Access date July 30, 2015).

Authors' recommendations/comments

BPS/IC is a challenging condition to manage and is likely made up of a number of clinical phenotypes which respond differently to the various treatments. It is a condition that requires a multi-disciplinary and multi-modal approach. Having a number of intravesical and oral agents available to each individual patient is important.

The availability of instillation agents depends on geographical location. Off-label use is common as a result of non-approval of agents by local drug approval agencies. Based on available evidence, DMSO, GAGs and Botulinum toxin appear to be safe with efficacy in the range of 60-80% however these figures are largely based on open-label, uncontrolled trials. Medium to long-term effects are variable.

Some studies have pointed out that BPS/IC patients with ulcer disease or a low capacity bladder have a less successful response to bladder instillations such as DMSO and Botox (16,49). Ongoing research to provide high quality data including subgroup analysis is needed. These trials need to be well-planned and executed, using comparator groups (either "placebo" or other agents) and using validated outcome tools to measure response to treatment.

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Footnote

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

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