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BPS/INTERSTITIAL CYSTITIS (D CASTRO-DIAZ AND Y IGAWA, SECTION EDITORS)

Intravesical Therapy for BPS/IC

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Abstract

Purpose of Review This manuscript gives a recent overview of intravesical treatments in patients with bladder pain syndrome/interstitial cystitis (BPS/IC). The newest data on GAG replenishment therapy, intravesical local anaesthetics, DMSO, botulinum toxin, experimental drugs, and ways of application are discussed.

Recent Findings The literature data show symptomatic therapeutic successes in a limited number of patients with most treatments discussed here. The heterogeneity of BPS/IC, the absence of clear knowledge of the cause in each patient, the different phenotypes included in the same research sample, the variability of dosage, and application frequency make interpretation of study results difficult. Treatment can aim at restoring a deficient GAG, to block the pain with local analgesics, and to lessen local inflammation, but it is uncertain from which treatment an individual patient will benefit most: trial and error are mostly used. Exclusion of many confusable diseases and Hunner lesions is the first step to indicate the treatment options with the most chance of success.

Summary The actual trial and error approach is the only available way so far for intravesical treatment in patients with BPS/IC. The overall results are acceptable, but a better understanding of the symptom syndrome and better phenotyping of BPS/IC patients will most probably improve the outcome in individual patients.

Keywords Bladder pain syndrome · Interstitial cystitis · Clinical practice · Diagnosis · Intravesical treatment · GAG layer

Introduction

The heterogeneity of bladder pain syndrome/interstitial cystitis (BPS/IC), a chronic symptom syndrome with a significant negative impact on the quality of life of patients, and the unknown causal mechanisms make diagnosis and treatment today difficult. Several possibly factors may be involved in the syndrome such as disturbance of the bladder wall barrier function, local inflammation, neuropathy, and genetic differences. The chronic state will cause peripheral and central sensitization, and creates many changes in the lower urinary tract, in the neurologic pathways, in the handling of sensory information in the brain, and other structures of the body, resulting in a changed clinical picture. The terminology, the evaluation, and the diagnosis of BPS/IC differ substantially among different clinics and in different countries preventing a global internationally accepted approach.

The significant advantages of intravesical treatment are that the substances are applied directly on the tissue to treat, and minimizing the likelihood of systemic side effects. Disadvantages and limitations of intravesical therapy are the need for repeated applications, a danger of provoking urinary tract infection, and the inability for patients to hold the solution long enough, significantly reducing the residence time of the drug in the bladder, thereby reducing the therapeutic effects. A further shortcoming of intravesical therapy may be the progressive dilution of the instilled drug solution owing to the rapid filling up of urine in the bladder, especially with high diuresis.

Several intravesical treatments are discussed.

GAG Replenishment Therapy

In the normal bladder, a glycosaminoglycan (GAG) layer lining the urothelium provides a barrier to protect the bladder wall from urinary toxins and pathogens. The GAG layer consists of different components such as the non-sulfated

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hyaluronic acid and the sulfated chondroitin sulfate and heparan sulfate/heparin. When the GAG layer is damaged, toxic elements may penetrate the tissue and cause the pain and inflammation characteristic of BPS/IC. Biopsy samples of patients with BPS/IC have shown that urothelium coating dysfunction is associated with multiple pathological features of parenchymal damage, including inflammation features [1•]. Correlations exist between urothelial damage, inflammatory infiltrate, and detrusor mastocytosis. However, cystoscopic severity score and grade and the histological findings can be uncorrelated in patients. Severe symptoms of BPS/IC have been seen when cystoscopy and histology were normal [1•]. Biopsy findings in the same symptomatic patients may be almost normal or severely pathological. These data are confusing and indicate clearly that there is considerable heterogeneity, both within the individual bladder and between patients, and that it may be necessary to take more biopsy samples from a patient to improve the accuracy of diagnosis. Dynamic contrast-enhanced magnetic resonance imaging (MRI), using T1-weighted MRI scans after injection of a gadolinium-based contrast agent, has been used to detect an increased bladder permeability [2, 3]. Uptake of the contrast agent was significantly increased in patients with BPS, but not in controls. Though not used routinely so far, the findings demonstrate that there are ways to show GAG deficiency and disturbed barrier function objectively.

When GAG layer deficiency is suspected (and in future hopefully objectively demonstrated), to try to restore the GAG layer by replenishing has been done with different solutions and substances like hyaluronic acid, chondroitin sulfate, the combination of hyaluronic acid and chondroitin sulfate, heparin, and pentosan polysulfate (PPS).

Chondroitin sulfate and hyaluronic acid can bind water which is key to their functioning as a permeability barrier by forming a gel-like layer on the apical cell membrane.

Exogenous GAGs can act to restore the GAG layer in BPS/IC. They can fill electrostatically empty areas, restore the leaking barrier layer, and reduce inflammation through a reduction in mast cells and other pro-inflammatory mediators [1•].

As our knowledge of the symptom syndrome increases, it becomes clear that a difference exists between cases with and without Hunner lesion [4•, 5]. Data on GAG replenishment in patients with Hunner lesion and with previous procedures are discussed further in the text.

Hyaluronic Acid and Chondroitin Sulfate

These substances are often used in GAG replenishment because they are both parts of the normal GAG superficial layer [1•]. Hyaluronic acid is used at a concentration of 0.8% and chondroitin sulfate in 2 different concentrations, 0.2% and 2% [1•].

Hyaluronic acid was shown to positively modulate the epithelial layer permeability, exhibit anti-inflammatory activity, and stimulate sulfated GAG synthesis in an inflammatory model of interstitial cystitis: induced secretion of the pro-inflammatory cytokines IL-6 and IL-8 was decreased (an overall 4–5-fold decrease in cytokine production) and sulfated GAG production was increased 2-fold, while permeability was decreased [6].

GAG replenishment has little or no effect in many, and this may be due to the heterogeneous nature of BPS/IC and the lack of detailed diagnosis ("leakers" and "non-leakers"). BPS/IC might also be a progressive disorder, and no responders may have reached a state beyond which response is no longer possible [1•]. Dosing may not be optimal, and the frequency of application insufficient. All of this will need much more research.

Long-term clinical experience together with an analysis of the available data supports the role of intravesical hyaluronic acid and chondroitin sulfate in the symptomatic treatment of BPS/IC, with evidence of symptomatic relief and improvement in QoL [1•].

A recent systematic review and meta-analysis analysed the efficacy of intravesical therapies available in Europe for the treatment of BPS/IC [7]. Only 19 of 345 published studies met the selection criteria, and a total of 801 patients were included, 228 of whom participated in 5 prospective controlled trials. All studies reported symptom improvement, including the placebo arms of the randomized controlled trials. However, the largest effect size for response rate was shown for high molecular weight hyaluronic acid [7]. In another recent meta-analysis, hyaluronic acid, alone or in combination with chondroitin sulfate, was shown to be effective in reducing pain and symptoms and improving QoL and other outcomes However, it was also noted that data from placebo-controlled trials and long-term studies were limited [8].

In an extensive literature review on Pubmed, the Cochrane library, and Embase with the results of the O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) and O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) as primary outcome criteria, combination therapy of hyaluronic acid and chondroitin sulfate ranked second in ICSI, third in ICPI, and first in the visual analogue scale of pain (VAS). Among regimens included for complication comparison, chondroitin sulfate was safer than other agents, with a probability of 78.5% [9].

When representative individual trials were reviewed, data showed support for the efficacy and safety of intravesical hyaluronic acid, chondroitin sulfate, or the combination of hyaluronic acid and chondroitin sulfate in patients whose BPS/IC symptoms did not respond to conservative or oral treatment.

Comparisons between products are conflicting. In a small study comparing hyaluronic acid with chondroitin sulfate, intravesical chondroitin sulfate was superior to hyaluronic

acid in terms of 24-h frequency, nocturia and interstitial cystitis problem index in patients with BPS/IC after short-term follow-up [10]. Caution is warranted because of the different non-specified patients in the group and different treatment schedules in literature.

Because of their different characteristics and properties, combining hyaluronic acid and chondroitin sulfate is considered a logical approach. Hyaluronic acid and chondroitin sulfate in combination have been compared to dimethyl sulfoxide (DMSO) in 110 patients with BPS/IC. Patients were treated with 13 weekly instillations of hyaluronic acid 1.6%/chondroitin sulfate 2.0% or DMSO 50%. The primary endpoint was a reduction in pain intensity at 6 months by visual analogue scale (VAS) compared with baseline. In the intention-to-treat population, both treatment groups had significant reductions in pain intensity ($p < 0.0001$). In the per-protocol population, treatment with hyaluronic acid/chondroitin sulfate produced a more significant reduction in pain intensity than DMSO (mean VAS reduction 44.77 ± 25.07 vs 28.89 ± 31.14, respectively; $p = 0.0186$). There were significantly fewer treatment-related adverse events for the combination therapy compared with DMSO [11].

The benefits of using a combination of substances or a combination of therapeutical measures are so far unclear. When GAG replenishment therapy is suboptimal, an oral therapy, such as oral PPS, an oral alkalinizing agent, and additional pain or muscle controlling drugs can be considered [1•]. The rationale for this needs further study. It was recently shown that hydrodistension and a sodium hyaluronate infusion once a week for 4 to 6 courses in 21 patients reduced the frequency of urination and reduced the pain threshold, and the improvements in clinical symptoms and score were maintained throughout 6 months of follow-up [12]. Taneja treated 91 patients with BPS/IC with a combination of oral PPS (100 mg TID) and an intravesical cocktail of heparin (25,000 IU) and hydrocortisone (200 mg) once a week, for 6 weeks. He found a response classified as good or excellent in 91.2% at 1, 3, and 6 months after the last intravesical instillation (excellent in 17.6% at 1 month, and 24.2% and 25.3%, respectively after 3 and 6 months, and good in 73.6% at 1 month, and 67.0% and 65.9%, respectively at 3 and 6 months). Only 8 of 91 patients reported an unsatisfactory response, while a good-to-excellent response was maintained by 83 of 91 patients for at least 6 months. There were 28 relapses in 13 patients between 9 and 40 months after treatment [13].

Previous treatment modalities, such as oral PPS, hydrodistension, fulguration for Hunner lesion, and the presence of Hunner lesions, are unrelated to the outcome of intravesical hyaluronic acid instillation in refractory BPS/IC. GAG replenishment therapy following initial fulguration can be successful in patients with Hunner lesion [14].

The optimum instillation schedule for GAG replenishment is not known, but there is a consensus that 6 weeks is too short to establish treatment success with GAG therapy [1•]. Today, a variety of instillation schedules are utilized by different clinics and in different countries. This is in part determined by cost (reimbursement/non-reimbursement by funders) and availability of ready-prepared formulations of intravesical therapies. Other issues for consideration are the benefits of extending the time for the instillation to be retained in the bladder beyond 2 h, the use of hydrophilic catheters, the need for antibiotic prophylaxis on instillation days, and the importance of excluding sexually transmitted diseases before commencing GAG replenishment therapy, especially in young women [1•]. Patients should be encouraged to regularly record their symptoms during treatment to document success or failure and permit the determination of an individually tailored installation schedule. Abrupt termination of instillations should be avoided [15].

Self-treatment can be considered an achievable goal once a stable condition has been achieved. It gives patients greater control over their condition and allows treatment to be administered when most needed in response to symptoms. Proper training of the patient or, if needed, patient's partner or another appropriate caregiver may help to overcome issues of age, poor eyesight, or infirmity and is supported by the personal clinical experience of patients managing their condition [16]. An interesting new approach presented by Lovász may be a catheter-free instillation, as it permits simultaneous treatment of the bladder and urethra. It also permits the avoidance of the adverse side effects of catheterization. A minimally invasive device for intravesical instillation, a urological syringe adaptor that fits on Luer-lock and Luer-slip syringes, has been developed and refined for use by both men and women, and over 98% of patients reported by Dr. Lovász and his colleagues could be successfully treated with this technique [16]. The same author has found that 70% of 52 patients diagnosed with BPS/IC had urethral pain, with or without bladder pain, ranging from a slight burning sensation to heavy, intolerable pain [17].

GAG replenishment therapy can be supplemented by symptomatic adjuvant approaches and prophylactic measures to relieve irritation, urethral pain, and bladder pain, such as following an alkalizing diet and drugs (pH 6.5–7.4), maintaining a diluted urine volume, reducing other drugs, avoiding antibiotics, and following a BPS/IC diet [18, 19]. Irritating agents, such as acidic urine (pH < 7), hyperosmotic (concentrated) urine, decomposition products of drugs, antibiotics, and volatile oils, aromatic compounds from herbs and spicy foods can, on the other hand, exacerbate symptoms [1•].

Long-term clinical experience and feedback from patient support groups validate the beneficial effects of intravesical GAG replenishment therapy [1•].

The term "bladder instillation" only defines a way of administering drugs to a patient. The ideal and most effective

medications, how long the instilled drugs should be kept in the bladder to ensure the best outcome possible, the correct dose and solution, and the frequency and duration of treatments to be used are still unknown, despite the reduction in symptoms noted in various studies [20•].

Heparin

Heparin is a polysaccharide and GAG layer enhancer [1•, 20•]. The combined use of intravesical alkalinized lidocaine with heparin was shown to give immediate and prolonged relief from BPS/IC, with a single vial of a 15-ml solution containing 200 mg of lidocaine and 50,000 units of heparin sodium buffered to pH 7.4 ± 0.2 with sodium bicarbonate (420 mg) in water [21].

Lidocaine

Lidocaine is a local anaesthetic with a short half-life of 1.5 to 3 h. It acts by blocking sensory nerve fibres in the bladder. Alkalinisation of lidocaine stabilizes a more significant percentage of the lidocaine into its non-ionized base form (33% vs 1–2% of unbuffered lidocaine at urine pH 5–6). As the bladder urothelium has a greater permeability compared with non-charged ions, alkalinized lidocaine has better absorption [22]. Described side effects of heparin-lidocaine instillation are in 30–50% headache, dizziness, lightheadedness, and bladder or urethral pain [20•]. Lidocaine proved safe and clinically effective at a dosage of 200 mg of alkalinized lidocaine daily for 5 days and 1-h retention [20•].

Resiniferatoxin

Shengzhuo et al. made a very recent review of eleven randomized controlled trials covering eight agents and with 902 patients enrolled. According to the results of the O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) and O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), improvement with 0.1 μM resiniferatoxin was more effective than other therapies [7].

DMSO

DMSO has been used already a long time because of its local anaesthetic, bacteriostatic, and anti-inflammatory properties [20•]. Lyer et al. compared DMSO plus triamcinolone with bupivacaine /heparin/ triamcinolone(B/H/T) [23]. DMSO treatment resulted in a greater percentage of overall improvement and a significant decrease in nocturia episodes compared with B/H/T. Reported side effects include increased urgency and dysuria, lethargy, nausea, fever, and haematuria, which was thought to be related to transient chemical cystitis; however, these were found to be low in frequency. The garlic odour after instillation is well known. The use of DMSO in animals has been linked to changes in their eye lenses, but no such link has been seen in clinical trials [24]. Long-term follow-up (median 60 months) suggests that DMSO/heparin/hydrocortisone/bupivacaine therapy might be moderately effective, but failure was more frequent in patients with pre-treatment reduced bladder capacity [25•, 26].

Sodium Pentosan Polysulfate (PPS)

PPS has been used for GAG replenishment in BPS/IC. It is currently the only oral therapy approved for BPS/IC in the USA, and the use of Elmiron ® is authorized in the European Union. Older studies have suggested that a solution of 200 mg (2 capsules) mixed with 30 ml of sterile normal buffered saline might result in significant improvements in pain and urgency, and in guidelines, a high level of evidence and a high grade of recommendation have been given for this treatment [20•]. Most recently, a possible relationship between long-term PPS exposure and the development of pigmentary maculopathy has been described with oral treatment [27•]. More research is necessary to elucidate further a causal relationship, the risk with an intravesical application, but caution is suggested when prescribing PPS, especially in patients with pre-existing retinal conditions [28].

Botulinum Toxin

Botulinum toxin A (BTX) is a promising treatment of BPS/IC. It has been shown to relieve pain, urgency, and frequency, and can improve the functional bladder capacity and urodynamics in refractory cases [28–30]. However, the success rate is variable, and most studies have small samples [31]. So far, there is no randomized placebo control study available. More studies are needed, but it is promising that studies so far show favourable results and little increase in post-void residual [32].

BTX is a neurotoxin with a high molecular weight. Adding liposome may help overcome the problem of delivery (see under).

Pilot Studies with Experimental Drugs

Tacrolimus

Tacrolimus has the same mechanism of action as cyclosporine A [33•].

Tacrolimus 0.1 mg/kg body weight dissolved in DMSO (50 ml 50% and solution of 1 ml DMSO in 24 ml/sterile water injected three times in 14 days) was effective in 54% of 24 patients without significant side effects. It has been used with liposome delivery (see under).

Platelet-Rich Plasma

Repeated intravesical injections with a monthly interval of 12 ml platelet-rich plasma extracted from 50 ml own blood were effective and safe, and improved pain and functional bladder capacity. It showed a positive result of a global response assessment [34•].

Tanezumab and Adalimumab

Tanezumab and adalimumab, capable of sequestering nerve growth factor (NGF), and tumour necrosis factor (TNF) have been proposed experimentally [35].

Liposomes

Liposomes are lipid vesicles composed of phospholipid bilayers surrounding an aqueous core and can incorporate drug molecules, hydrophilic and hydrophobic, and show greater uptake into cells via endocytosis. They can form a protective lipid film on the urothelial surface. Liposomes 80 mg/40 ml distilled water once weekly has been previously described to be successful and safe in a small group pilot study [36]. A study has been done with liposomal BTX and with tacrolimus and was judged to have a favourable effect [33•, 35, 36].

Continuous Intravesical Lidocaine (LIRIS) This treatment has shown little difference with placebo in efficacy and safety [37].

AQX-1125, a novel SHIP1 activating compound, is experimental [35].

Conclusion

For the intravesical treatment of BPS/IC, several items must be solved.

In published studies, it has been proposed that the instillation should be kept in the bladder for a minimum of 30 min and a maximum of 45 min. However, whether more prolonged exposure of the intravesical drugs with the urothelium affects the outcomes still needs to be proven. Various frequency regimes of bladder instillations have been described, ranging from a single treatment to 3–5 times a week for a period of 1–6 weeks to 12 months. The absence of a proper way to phenotype the patients makes that treatments are given in a trial and error fashion. The very heterogenic populations included in studies may count for the differences in outcome. Several substances are used. Randomized controlled trials are mostly missing.

Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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