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Interventional Treatments for Bladder Pain Syndrome

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Abstract

Patients with BPS persistent and unacceptable symptoms despite oral and/or intravesical therapy are candidates for more aggressive modalities. Many of these are best administered within the context of a clinical trial if possible. These may include: neuromodulation, intradetrusor botulinum toxin, oral cyclosporine and other anesthesic techniques. The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacities of the bladder or diverting the urinary stream. In this paper a review of interventional treatment´s clinical evidence is made and shows how to improve symptoms in refractory BPS.

Keywords: Bladder painful syndrome; Chronic bladder pain; Interstitial cystitis

Introduction

Although underlying pathophysiology of painful bladder syndrome/interstitial cystitis (PBS/IC) is not completely understood, it involves urothelial permeability changes primarily, along with mast cell activation and neurogenic inflammation [1]. In PBS/IC condition, damage to the protective bladder lining leads to impaired urothelial cell barrier function. Consequently, urinary solutes penetrate the epithelium and activate sensory nerve endings, leading to the manifestation of inflammation and pain [2]. Consistent with this theory, bladder epithelial cells in PBS/IC patients are shown to produce anti-proliferative factor (APF) [3], which may further contribute to the impaired urothelial cell barrier. Moreover, urothelial cells in PBS/IC patients fail to release prostaglandin E2 (PGE2), which is crucial for the protection and repair of the urothelium [4]. Other bladder epithelial abnormalities reported in PBS/IC include abnormal cellular architecture as revealed by electron microscopy [5] and abnormal uroplakin expression as assessed by reverse transcriptase PCR [6]. Mast cell may play a central role in PBS/IC pathophysiology: patients have increased number mast cell along with higher percentage (70%) of activated mast cells versus 10% in healthy controls [7]. Moreover, compounds that are indicative of mast cell activation such as Interleukin 6 (IL-6), histamine, and tryptase are increased in the urine of PBS/IC patients [8]. Interestingly, Tamm-Horsfall protein concentration in the urine of PBS/IC patients may not differ from healthy controls, but it is qualitatively different containing less sialic acid [9]; this altered protein may thus be involved in PBS/IC pathogenesis.

Neurogenic upregulation may also play a role in the pathogenesis of PBS/IC. The purinergic pathway has been shown to be upregulated in urothelial cells from PBS/IC patients [10], with peripheral and central neural upregulation [11]. However, whether the neurogenic inflammation that characterizes PBS/IC is the cause or the result of other previous events is yet unresolved.

The condition of PBS/IC could result from different environmental triggers in a genetically susceptible individual [12]; this approach may explain its increased prevalence among first-degree relatives and monozygotic twins. In this context, PBS/IC could be considered a clinical phenomenon in a genetically susceptible individual, where an environmental trigger such as trauma or infection could promote genetic events leading to an inflammatory response [13].

Treatment

First line of treatments applicable to all the affected patients includes awareness, education, self-care, and stress and pain management. Most patients may require additional therapy and oral medications or bladder instillations or pelvic floor physical therapy all considered second line options. Bladder instillations represent interventional treatments which are more commonly applied in combination therapy. Manual pelvic-floor physical therapy actually has the strongest evidence for efficacy, although availability and cost can present barriers to patients. Should these fail to yield the desired therapeutic effect, more invasive interventions, such as cystoscopy with hydro distention or sacral nerve stimulation may be opted. The use of cyclosporine or bladder injections of botulinum toxin is also alternative options available for select refractory patients. It should be noted that, apart from.

Dimethyl Sulfoxide (DMSO)

Mechanisms involving DMSO facilitates dissolution of collagen and degranulation of mast cells and it helps to reduce inflammation relax muscles and mitigate pain. Only one randomized study, reported by Peeker et al. [14], showed pain reduction in ulcer type IC patients, although no improvement was observed in maximum bladder capacity. In a non-randomized controlled study, Perez-Marrero et al. [15] reported that, 53% of the patients showed remarkable improvement in subjective evaluation (placebo 18%), and 93% in objective evaluation (placebo 35%). Previously, an improvement rate as high as 80% has been reported in case series and retrospective studies. With regard to side effects after instillation of DMSO, most patients sense a garlic-like

odor, which disappears within a day, and about 10% of patients reported bladder irritation symptoms which resolve with or without symptomatic treatment. It is hypothesized that these transient exacerbations occur as the result of mast cell degranulation. The number of side effects was considering as small. Negative effects on bladder compliance have been noted upon absorption of other drugs instilled simultaneously, which could be a source of side effects [14-26].

The instillation method is generally as follows: 50 cc solution of medical grade 50% DMSO is instilled into the bladder. For avoiding pain following instillation, local anesthesia (e.g., 20 ml of 2% lidocaine solution) may be instilled. Average retention time is considered to be 10-20 min [24]. The instillation is performed weekly during a period of 6-8 weeks. After an initial course, treatment is suspended until symptoms recur, another 6 week course, followed by monthly maintenance could be initiated. Although, there is no upper limit for the duration of the treatment, the long-term effect is still unknown. DMSO solution instillation has not been approved yet in Japan.

Heparin

A slight chance of bladder hemorrhage is there due to repeated catheterization. It is believed that a deficiency or abnormality of glycosaminoglycan (GAG) causes inflammation of the bladder by increasing the permeability of the bladder mucosa as secondary effect, leading to the pathologic cascade of BPS. Heparin has similarities to the GAG layer of the bladder. Instilled into the bladder, theoretically it might replace the damage of the GAG layer. Kuo [27] reported that the bladder capacity at initial desire to void and maximum bladder capacity improved significantly. According a previous report, Parsons et al. [28], the symptoms were reduced by 56% in patients treated 3 times weekly for a period of 12 weeks. However, there were no randomized and comparative studies to provide conclusive evidence. It is thought that in combination with DMSO, it prolongs the response to DMSO treatment [29].

In the case of hematuria patients, however, it may exacerbate local hemorrhage. The instillation method has not been standardized. Parsons et al. [30] recently reported that when 40,000 units of heparin in combination with 1% to 2% lidocaine were instilled 3 times a week for a period of 2 weeks, about 80% of efficacy was obtained. There were no upper limit for the duration of the treatment, but a long-term effect is yet unknown.

Hyaluronic Acid

Hyaluronic acid, like heparin, is a mucopolysaccharide that could theoretically repair a damaged GAG layer of the bladder mucosa. Several reports indicated its efficacy [31-36]. In the spring of 2004, Seikagaku Corporation reported double-blind, placebo-controlled, multi-center clinical study of their hyaluronic acid preparations at the rate of 40 mg or 200 mg per cc respectively which did not show any significant improvement of sodium hyaluronate when compared to placebo (unpublished data). A non-placebo-controlled study has demonstrated a favorable effect of hyaluronic acid on pain reduction [32]. Forty-eight patients with typical symptoms and a positive sensitivity test to 0.4 M potassium were treated with weekly instillations of 40 mg hyaluronic acid for a period of 10 weeks. Visual analogue scale scores showed symptomatic relief due to hyaluronic acid therapy, irrespective of bladder capacity. The improvement was particularly evident in patients with a reduction in Cmax of <30% compared to patients with a reduction by <30% with 0.2 KCl solution (P=0.003). A recent interventional study from China suggested a prolonged effect of bladder distension when combined with instillation of hyaluronic acid [37].

Chondroitin Sulfate

Chondroitin sulfate is another mucopolysaccharide. Its mechanism of action may be similar to hyaluronic acid or heparin and its benefit has been first reported in the year 2002 [38] as well as in another trial when used in combination with hyaluronic acid [39]. Steinhoff [40] treated 18 patients with 40 ml solution, instilled intravesically weekly once for a period of 4 weeks and then monthly once for 12 months. A total of 13 out of 18 patients responded to treatment within 3 to 12 weeks. A total of 6 out of 13 patients representing 46% had a good response, about 2 out of 13 (15.4%) had a fair response, around 4 out of 13 (30.8%) had a partial response and 1 out of 13 (7.7%) showed no response. In a second trial [41], 24 refractory patients with BPS/IC were treated with high dose (2.0%) of chondroitin sulphate instillations twice weekly for 2 weeks, then weekly with 0.2% solution for 4 weeks, then monthly and thereafter for 1 year. The average symptom improvement reported in 20 patients completing the trial was 73.1% ranging from 50% to 95%. A large multicenter open study was reported, where chondroitin sulphate instillation was effective and well tolerated in the therapy of various chronic forms of cystitis associated with a possible GAG layer deficit including BPS [41]. A total of 65 patients with IC/BPS were treated in a prospective, randomized, double-blind, inactive vehicle-controlled 12 weeks follow-up study (6 weeks treatment, 6 weeks follow-up). At the primary end point analysis after 7 weeks, 22.6% of the vehicle control group were responders compared with 39.4% of the active therapy group (P>0.05) [42]. A follow up randomized placebo-controlled trial with 98 female patients showed only minor improvements in IC/BPS symptoms and pain, and failed to demonstrate a statistically significant drug effect *vs.* placebo [43].

Pentosan Polysulfate

Pentosan polysufate (PPS) is a mucopolysaccharide similar to heparin. A randomized controlled trial found benefits in 4 out of 10 patients with PPS treatment *vs.* 2 out of 10 on placebo [44]. A more recent placebo controlled study comprising of 41 patients found that the addition of intravesical weekly PPS to an oral regimen of PPS improved results.

Vanilloids (Capsaicin, Resiniferatoxin)

Its mechanism of action is a desensitizing bladder afferents. Resiniferatoxin (RTX) is considered to have a stronger action than capsaicin with desensitizing C-fibers more quickly and causes less bladder irritation. The efficacy was noticed in small clinical trials [45-49]. No severe side effects were reported. A randomized multicenter placebo-controlled clinical trial of RTX failed to demonstrated benefit *vs.* placebo [50].

Bacillus Calmette Guerin (BCG)

Peters et al. [51], in a double blind randomized study, reported a 60% improvement in efficacy when compared to 27% placebo response with good long-term results at 27 months. About 65% patients experienced burning sensation, 41% reporting irritation of the bladder,

and 35% had pelvic pain. One patient was reported to have dropped out due to joint pain. A very large, multicenter randomized placebo controlled trial conducted by the National Institute of Diabetes, Digestive, and Kidney Disorders failed to identify benefit of BCG, although the side effect profile was surprisingly similar to that of placebo [52].

Oxybutynin

Barbalias et al. [53] observed significant improvement. When combining intravesical instillation with bladder training. Randomized clinical trials are lacking.

Lidocaine

Lidocaine is a local anesthetic that relieves pain by blocking sensory nerves in the bladder. Four articles [54-58] reported electromotive drug administration (EMDA) of lidocaine. Using EMDA, ionized lidocaine was actively introduced into the bladder using an electrical current. Three articles reported that lidocaine and dexamethasone were instilled following hydro distention. According to the report by Rosamilia et al. [57], 85% of the patients had a good result, with maintenance of 6 months in 25%. A total of 102 adult patients comprising of 99 women with a clinical diagnosis of BPS were randomized from 19 centers in the USA and Canada to receive a daily intravesical instillation of alkalinized lidocaine or placebo (double-blind), for 5 consecutive days. Treated patients had significant sustained symptomatic relief for upto 1 month [58].

Botulinum Toxin

Botulinum toxin type A (BTX-A) acts by binding to the nerve endings within muscles, blocking the release of acetylcholine, and probably other neuro-transmitters, to modulate muscle contraction and reduce the sensitization of sensory nerve endings [59]. To ascertain effect of repeat injections, a total of 13 patients were followed up for 2 years, while 58 injections were administered with a mean of 4.8 ± 0.8 injections per patient. The mean interval between two consecutive injections was 5.25 ± 0.75 months. At 1 and 4 months follow-up, 10 patients reported a subjective improvement. Mean Visual Analogue Scale (VAS) scores, mean daytime and night-time urinary frequency decreased significantly. The three non-responders to the first intravesical treatment session underwent further treatment, 3 months later with satisfactory results. At 1 and 2 years follow-up, the beneficial effects persisted in all patients [60].

These results were in contrast with those in another study by Kuo [61] on BTX-A (botulinum toxin A) in 10 patients with BPS. One hundred units were injected subrotherially into 20 sites in five patients, while 100 U were injected into the trigone in the remaining five. None of the patients became symptom-free.

In a randomized controlled trial (RCT), Kuo and Chancellor [61] analyzed the difference between hydrodistention and hydrodistention plus intravesical, sub-mucosal BTX-A. Of the 67 patient, 44 were divided in two groups: one received 200 U and the other 100 U, and cystoscopic hydrodistention was performed after 2 weeks. The remaining 23 patients received hydrodistention only. There was symptomatic improvement in all groups. However, in the hydrodistention group, 70% had recurrence of previous symptoms after the first month, while in the BTX-A-treated groups; there was improvement of VAS, functional bladder capacity and cystometric bladder capacity at 3 months. At 12 and 24 months, the results in the active group were 55 and 30% versus 26 and 17% in the hydrodistention group, respectively.

Neuromodulation

Sacral nerve stimulation (SNS) involves implanting permanent electrode(s) to stimulate S3 or S4 roots. One study [62] showed that temporary stimulation was effective in 73% of 15 women with refractory BPS. Mean voided volume during treatment increased and mean daytime frequency, nocturia and pain decreased significantly. In a report in 2003, Comiter et al. [63] prospectively investigated the effect of SNS on a series of 17 patients with refractory BPS. At an average of 14 months follow-up, mean daytime frequency, nocturia and mean voided volume improved significantly. The average pain decreased from 5.8 to 1.6 points on a scale of 0 to 10 and the Interstitial Cystitis Symptom (ICS) and Problem Index (PI) scores decreased from 16.5 to 6.8 and 14.5 to 5.4, respectively. Of the 17 patients, 16 patients (94%) with a permanent stimulator demonstrated sustained improvement in all parameters at the last postoperative visit. In another paper [64] the authors applied percutaneous sacral nerve root stimulation on 33 patients with refractory interstitial cystitis. Statistically significant improvements were seen in pain and urinary symptoms. SNS reduces the usage of analgesics in PBS as showed Peters et al. [65], although the dose reduction was modest (36%) and only 4 out of 18 discontinued the narcotics.

Zabihi et al. [66] reported more extensively stimulated S2-S4 by implanting electrodes into epidural space through sacral hiatus. A total of 23 of 30 (77%) patients had successful trial stimulation and were permanently implanted. Among these patients, the symptom and pain score were improved significantly by 35% and 40%.

In a first prospective, comparative, single-blind, crossover trial of sacral nerve stimulation (SNS) versus pudendal nerve stimulation (PNS) for patients with BPS (n=22), PNS gave an overall 59% improvement in symptoms, whereas SNS gave an overall 44% improvement (P=0.05) [67]. Most patients who tested both a sacral and pudendal electrode chose PNS as the better site. Follow- up showed marked improvements in voiding variables and validated BPS symptom questionnaires. Over 90% of patients treated with neuromodulation stated that they would undergo implantation again [67].

The longest follow-up study published is a retrospective study comprising of 78 patients treated from 1994 to 2008. Permanent sacral neuromodulation implantation was performed in patients who showed at least 50% improvement in their symptoms with a temporary peripheral nerve evaluation test. Good and long-term result of sacral neuromodulation was seen in 72% of the patients. The explanation rate was 28%. The most frequent reason for explanation was poor outcome (54% of the failed patients). The revision rate was 50% [68].

Experimental Therapies

Hyperbaric oxygen (HBO)

Only three studies have published encouraging results. In one study, 11 cases showed significant improvements in pain, urgency, and frequency of voids and O'Leary-Sant Interstitial Cystitis Score/Problem Index (OSICSI/PI) scores [69]. At five sessions per week, these patients had received 2 to 4 weeks of HBO treatment at a rate of 2.0

atmospheres absolute (ATAs), and the response to treatment was maintained for up to 2 years. This study was a continuation of two cases with similar results that had already been published by the same author [70]. Van Ophoven et al. presented six cases in which HBO was applied under conditions similar to the study with 30 sessions per patient and 2.5 ATAs. With a mean follow-up of 12 months, improvement in the void frequency and in pain was reportedly observed [71]. Out of 20 patients with mean age of 47.6 years (SD=18.4), 14 patients experienced clinical improvement after DMSO treatment in all of the evaluated symptoms ($P<0.05$; 95% CI). After the second phase, all patients who received HBO had a more substantive and prolonged maintenance of the DMSO effects [72].

Surgical Therapy

Hydrodistention

First bladder hydro distention experience was reported by Franksson in the year 1957. It was a retrospective series of 33 patients, with symptomatic improvement in all, and lasting up to 1 year in 7 patients [73]. More recent literature reported poor results with only a minority of patients reporting a little improvement in symptoms for a relatively short period of time [74].

Transurethral resection (TUR)

Results of transurethral resection were originally reported by Greenberg et al. [75] and Fall [76]. The retrospective results of this first treatment in 116 patients with Hunner's lesion from Fall's Swedish clinic were later reported by Peeker et al. [77]. A total of 92 patients experienced alleviation of their symptoms. Average duration of symptom alleviation was 23 months ranging from 0 to 180 months. The largest series ever published comprised of over 39 BPS patients wherein, 19 out of 39 had Hunner's lesion. Out of the 19 patients with Hunner's lesion, 17 reported good pain relief lasting between 6 and 18 months. In the 20 patients without Hunner's lesion, reddened areas in the bladder were photocoagulated with the Neodynium: Yag laser. 13 patients felt marked improvement of symptoms but time to symptom recurrence was not reported. This series was extended to 76 patients with Hunner's lesion (BPS European Society for the Study of Interstitial Cystitis, ESSIC type 3X) experienced symptom improvement; 12 patients had relapse within 18 months. Of patients with BPS ESSIC type 1 or 2, 20 out of 49 improved, but 10 required further therapy within 1 year [78].

Payne et al. reported study on 14 patients with Hunners lesion treated by cystoscopic ablation. 8 patients became symptom free and 4 patients improved symptomatically by more than 50%. 4 patients had symptomatic recurrence with improvement after repeated ablation [79].

Peripheral denervation

Worth [80] followed patients up to 7 years and found bladder areflexia to be a significant complication of this procedure. Patients had to use Credé technique or even be on intermittent self-catheterization. Albers & Geyer has reported symptom recurrence after 4 years in most of the patients [81].

Sympathetic denervation

Immediate results were very good; however Nesbit has showed that the long term results were short lived [82].

Parasympathetic denervation

Moulder and Meirowsky were used S3 neurectomy in 3 patients with good long term follow-up. Larger series were reported by Milner and Mason but results after five years were not encouraging [83-85].

Bowel surgery

It is consider only if patient was a no responder to previous treatments. Bladder augmentation cystoplasty has been commonly used for refractory BPS for 50 years. Later publications were less sanguine with good results varying up to 100% [86,87] or 25% [88]. Cystoplasty is usually done with or without bladder resection. Cystoplasty alone was reported as early as 1967 by Turner-Warwick and Ashken [89], advocating augmentation with removal of the diseased tissue. Several subsequent studies indicated that cystoplasty with subtrigonal cystectomy offers better results than without subtrigonal cystectomy [90-92]. Experiences with different bowel segments have been reported in numerous articles with level 4 evidence: Ileum, [93-96] leocecum, cecum [97-101], right colon [102-104] and sigmoid colon bowel segments with regard to outcome except for gastric tissue substitution.

Cystoplasty with supratrigonal resection(i.e., trigone-sparing) has been reported in various studies. Kontturi et al. [90] used segments of colon and sigmoid colon in 12 cases with 100% symptom-free outcome in the five patients with sigmoid colon over 4.7 years of follow-up. Two out of seven cases augmented with colon required ileal conduit and cystectomy. Van Ophoven et al. [104] reported the long-term (mean 5 years) results of orthotropic substitution enteroplasty in 18 women with BPS, using ileocecal (n=10) or ileal (n=8) segments with only two failures. In the group [105] augmented with ileum, three patients required self-catheterization and one a suprapubic catheter.

Cystoplasty with subtrigonal cystectomy were reported [106-110]. Because of the need of ureteral reimplantation, it is associated with some risks of urine leakage, urethral stricture and reflux.

Urinary diversion with or without total cystectomy and uretherectomy

This is the ultimate, final and most invasive option. Techniques include simple or continent urinary diversion. Simple urinary diversion with formation of an ileal conduit is the most common surgical treatment for BPS [108]. Bladder defunctionalization alone produced symptom relief in several reports [109-111]. Often diversion is performed as a next step after unsuccessful bladder augmentation. To avoid further bowel resection, a bowel segment used for cystoplasty can often be converted to a conduit [112]. In some patients, chronic inflammatory changes have been seen in the cystoplasty pouch resembling interstitial cystitis [113] preventing one from using this technique. Similar bowel changes however, have been described when cystoplasty was performed for pathology other than interstitial cystitis, suggesting that these pathologic findings are not a direct result of the exposure of bowel to BPB urine [114]. Relatively good responses to diversion without cystectomy have been reported in small series [115,116].

Conclusion

BPS initial treatment includes patient education, dietary manipulation, nonprescription analgesics and stress reduction. When conservative therapy fails or symptoms are severe and conservative management is unlikely to succeed, intravesical treatment can be performed.

It is recommended to initiate a single form of therapy and observe results, adding other modalities or substituting other modalities as indicated by degree of response or lack of response to treatment.

Those patients with persistent, unacceptable symptoms despite oral and/or intravesical therapy are candidates for more advanced modalities. Many of these are best administered within the context of a clinical trial if possible. These may include neuromodulation, intradetrusor botulinum toxin, oral cyclosporine and other anesthetic techniques.

The last step in treatment is usually some type of surgical intervention aimed at increasing the functional capacity of the bladder or diverting the urinary stream. Urinary diversion with or without cystectomy has been used as a last resort with good results in selected patients. Augmentation or substitution cystoplasty seems less effective and more prone to recurrence of chronic pain in small reported series.

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