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Current Recommendations for Bladder Instillation Therapy in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome

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Abstract Bladder instillation therapy refers to the direct introduction of medication into the bladder and is a common treatment modality for patients with interstitial cystitis/bladder pain syndrome (IC/BPS) who have failed conservative and oral therapies. The current American Urological Association (AUA) recommendations list three medications as options for IC/BPS instillation therapy: dimethyl sulfoxide, heparin, and lidocaine. The purpose of this review is to examine the evidence behind the recommendations for these medications. We also examine several historical or experimental therapies that do not hold recommendations but are still used on rare occasion. Finally, we discuss our bladder instillation strategies as well as potential future research and development in intravesicular therapy.

Keywords Interstitial cystitis · Bladder pain syndrome · Instillation therapy · Intravesicular dimethyl sulfoxide · Intravesicular heparin · Intravesicular lidocaine

Introduction

Bladder instillation therapy refers to the direct introduction of a treatment agent into the bladder via a catheter. Generally these treatments are used as third line therapies and are reserved for patients who fail conservative management as well as oral medication (amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate). While various intravesicular therapies have been used to treat interstitial cystitis/bladder pain syndrome (IC/BPS) since the mid-1900s, many have not been proven to be appropriately safe and effective. The following chapter reflects the current American Urological Association (AUA) guidelines on the use of bladder instillation therapy for the treatment of IC/BPS [1••]. Table 1 shows the common instillations and the grade of evidence for each. This grade is based upon number of studies, study design, and total amount of data. Grade A is the highest level of evidence and is based on well designed randomized clinical trials with narrow confidence intervals or overwhelming evidence in some other form. Grade B is intermediate evidence and is based on either lower quality randomized clinical trials or when data from randomized clinical trials is heterogeneous. Finally, grade C evidence is based upon observational study, unsystematic clinical experience, or randomized clinical trials with serious design flaws. Dimethlyl sulfoxide, heparin, and lidocaine are all considered acceptable options and the balance of benefit versus risk in their use must be decided on an individual patient basis.

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Dimethyl Sulfoxide (DMSO)

DMSO is an organosulfur compound with chemical formula $(CH3)_2SO$. This very old compound was first discovered in 1866 and first used in veterinary medicine. It has been a mainstay treatment in IC/BPS ever since researchers at the Cleveland Clinic discovered its efficacy in the treatment of genitourinary inflammatory disorders in 1978 [2]. Although the exact mechanism by which DMSO alleviates IC/BPS is unknown, it is believed to work through several mechanisms: studies have suggested that it may act by reducing inflammation [3], causing detrusor relaxation [4], or dissolving collagen, as well as by acting as an analgesic [5]. DMSO may also cause temporary urothelial injury [6] and therefore may allow for better penetration of other agents. As such, DMSO is often given as part of a "cocktail" in a multimodal regimen [7]. These cocktails include some combination of DMSO, heparin, lidocaine, sodium bicarbonate, and/or steroid, but no combinations have been proven more effective than others. The

Table 1 Types of bladder instillation therapies

Treatment	Grade of evidence
Dimethyl sulfoxide (DMSO)	C
Heparin	C
Lidocaine	B
Resiniferatoxin	-A (recommended against)
Bacillus Calmette-Guerin (BCG)	-A (recommended against)
Silver nitrate	Historic
Clorpactin	Historic

AUA rates the quality of evidence as high, moderate, or low (A,B or C). Treatments listed as historic are referenced only for their place in urologic history and are rarely seen today

general DMSO only regimen involves initial 50-mL doses weekly for 6–8 weeks, followed by 50-mL maintenance doses every two weeks for 3–12 months [5].

Evidence for the use of DMSO in IC/BPS spans the spectrum in quality. As such, DMSO currently holds an evidence grade C recommendation [1••]. While several observational and prospective studies speak to the effectiveness of DMSO [8–11], the strongest evidence has been generated by two randomized clinical trials from 1988 [12•] and 2000 [13•]. In the first study, 33 patients (30 women and 3 men) with diagnosed IC were randomly assigned to either the experimental group—where they were to receive four treatments 50 mL of 50 % DMSO biweekly with 15-min retention times—or the control group, which was to receive saline. The patients were evaluated based upon two criteria. First, blinded evaluators evaluated the patients based upon urodynamic and voiding studies in order to generate objective data points. Second, subjects also recorded their own subjective response. The results were that 93 % of patients receiving DMSO objectively improved during the trial period, as opposed to 35 % of the controls. Furthermore 87 % of patients in the experimental group subjectively improved, versus 59 % of the controls. A total of five adverse events were recorded during this study, with the only two major events occurring during the instillation of saline.

In the second major randomized clinical trial investigating the effectiveness of DMSO for IC, Peeker et al. compared the efficacy of DMSO against that of bacillus Calmette-Guerin (BCG) [13•], another potential intravesicular treatment. Here, 21 patients categorized as having either ulcerating or non-ulcerating IC were randomized to receive either DMSO or BCG instillations, with the DMSO again being administered in 50 % solutions at six weekly instillations. While the results of this study were less impressive than that of the prior study, they still spoke to the efficacy of DMSO: There was a significant decrease in urinary frequency in patients with ulcerating IC from the DMSO group (though not in patients with non-ulcerating disease), and there was a significant decrease in the pain scores in both ulcerating and non-ulcerating disease. These results heavily contrasted the BCG group, where no improvement was seen. This study reaffirmed the use of DMSO, in addition to adding further evidence against the now defunct use of BCG.

Heparin and Glycosaminoglycans

Heparin is the highly sulfinated glycosaminoglycan (GAG) best known for its use as an anticoagulant. In addition to its hematological uses, heparin has also been adopted as an intravesicular treatment for IC/BPS. The theoretical benefit of heparin in these patients is derived from the histopathogical changes exhibited in IC: when diseased urothelium exhibits a loss of its endogenous proteogycans [14, 15]. Heparin has the potential to act as an exogenous GAG, and may be able to replace some of the urothelium's natural function [16, 17]. Heparin also demonstrates a variety of other potentially beneficial effects, including anti-inflammatory, fibroblast proliferation inhibition, angiogenesis, and smooth muscle cell proliferation, and therefore may act in IC/BPS by multiple mechanisms [18].

Unfortunately, evidence for the use of heparin in IC/BPS is not as robust as that for DMSO. As of now, no randomized clinical trials have yet been completed comparing the efficacy and safety of heparin to placebo. Still, heparin holds an evidence grade C recommendation based on several observational studies [1••]. In the first study, Parsons et al. used 10,000 units of heparin in 10 ml sterile water, three times per week with retention time of 1 h [19•]. Patients were treated for 3 months, with an additional nine months available to those who achieved good remission. A total of 48 patients were chosen to receive this therapy, and 27 (56 %) achieved good clinical response. Furthermore, 23 of 27 chose to continue maintenance treatment for three months, with 20 of them remaining in remission. Of those 20, 16 then continued maintenance for an additional six months, with 15 remaining in remission. Parsons has also continued his work with multi-drug cocktails, combining heparin and lidocaine with comparatively good results [20]. Other groups have had similar results [21, 22]. Currently a multi-institutional, placebo controlled randomized clinical trial is ongoing in order to better assess the effectiveness of heparin (here in a pre-mixed formula with buffered lidocaine).

With the success of heparin, other GAGs have also been considered for use in treating IC/BPS, but none have proven successful. The most common is the nonsulfinated GAG hyaluronic acid. Although it sees some use in Europe and Canada, hyaluronic acid has not been proven to be effective in any randomized trials. The drug actually underwent two multi-center, double-blinded, placebo-controlled industry funded studies in 2003 and 2004, and neither demonstrated significant efficacy [23, 24]. Another possible GAG is

pentosan polysulfate (PPS). While this GAG has also been shown to have positive efficacy in a randomized, placebo-controlled study comparing oral and intravesicular PPS against oral PPS and intravesicular placebo [25], there is considerable debate as to if the improvement was the result of the intravesicular PPS, or the combination of oral PPS and the intravesicular lidocaine that all patients received [26]. As such, its use is still considered investigational. Finally, chondroitin sulphate is another GAG that has shown some potential in observational studies, but has not yet been evaluated in a randomized clinical trial [27].

Lidocaine

Lidocaine is a common topical anesthetic that has been used in a wide variety of pain syndromes, and the use of such anesthetics has long been practiced in the treatment of IC/BPS. It is given in a wide array of different formulations and concentrations, and recently has seen increasing use in combination with an alkalizing agent in order to avoid ionization within the acidic urine and better penetrate urothelium [28•]. Unfortunately, the relief granted by lidocaine is rarely long lasting (longer than 2 weeks). Currently researchers are attempting to remedy this problem with implantable lidocaine eluding devices, and initial results are positive [29].

Lidocaine currently has an evidence grade B) [1••], with several good studies demonstrating its efficacy alone or in conjunction with other medications. In one large multi-center, double-blind, placebo-controlled study, 102 patients were randomized to receive either a combination of 200 mg lidocaine, alkalinized with a sequential instillation of 8.4 % sodium bicarbonate solution or saline, for 5 consecutive days with 1-hour retention [28•]. Significantly more patients in the experimental group saw improvement in their symptoms than in the control group (30 % versus 9.6 % respectively at day 3). However, as time progressed to day 10, the findings ceased being significant, perhaps speaking to the short term gains of lidocaine. An open-label phase followed the placebo control phase in this trial, where 54 % of patients at 3 days and 48 % at 10 days reported significant improvement. As previously mentioned in this chapter, other studies involving lidocaine combinations. including heparin [20] and PPS [25], have also had positive results.

Other Intravesicular Treatments

While the previous sections describe all the therapies currently listed within the AUA guidelines, there are a number of other treatments that have been used in attempts to relieve the symptoms of IC/BPS. Some of these treatments are historical

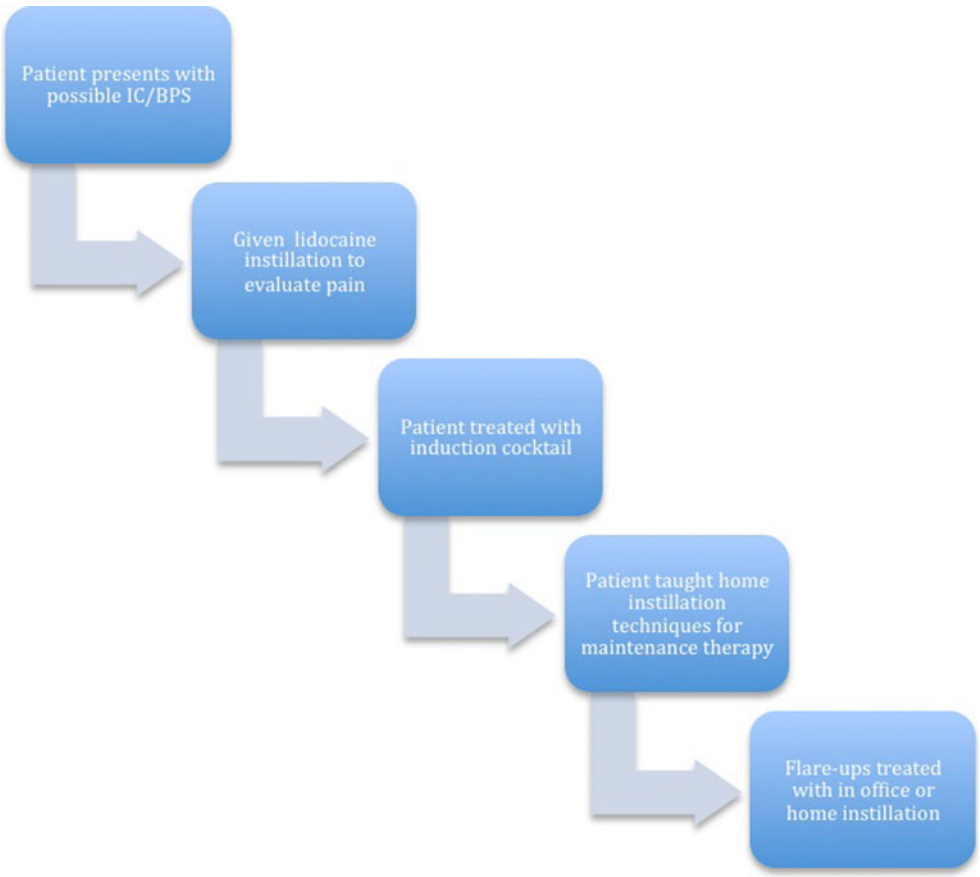

Fig. 1 Treatment protocol

and have been found to be ineffective, while others lack evidence and are not yet recognized as having clinical value. The oldest intravesicular treatment silver nitrate. Originally marketed as *Argyrol*, this drug dates back to the late nineteenth century and was originally marketed as a pre-antibiotic urethral treatment for gonorrhea [24]. Although this treatment is rarely seen in modern times, due to the severity of side effects, a recent study did demonstrate the anti-inflammatory effects of silver nitrate in a rat bladder model, raising the possibility that such compounds might still be effective [30]. Another such rarely seen treatment is clorpactin. Clorpactin is an umbrella name for a group of closely related highly reactive chemicals that incorporate hypochlorous acid in a buffered base. The positive effects are theorized to result from detergency as well as the oxidizing effects of the acid. Due to the pain associated with instillation, this treatment is rarely seen in the United States.

Currently there are two drugs that the AUA has assigned –A recommendations (should not be offered, risks and burdens outweigh benefits). The first is resiniferatoxin (RTX), a highly potent analogue of capsaicin. While early observational studies suggested the potential use of this treatment [31], two large randomized clinical trials failed to find any benefit of RTX versus placebo [32, 33]. Moreover, both studies found high rates of adverse events, mainly pain following instillation.

The second therapy with a –A recommendations (should not be offered, risks and burdens outweigh benefits) is bacillus Calmette-Guérin (BCG) [1••]. This common bladder cancer treatment originally saw great potential in the treatment of IC/BPS: The first randomized clinical trial involving BCG demonstrated a 60 % response rate, compared with a 27 % response rate in the placebo group, with equal toleration between groups [34]. Even more impressively, 8 of the 9 patients who remained within this study continued to have excellent response at the long-term 27-month followup [35]. While this study generated high hopes for BCG, they unfortunately did not pan out. This original study only involved 30 subjects, and a later study with significantly higher power (265 subjects) failed to generate significant results, with BCG patients only exhibiting mildly better outcomes than controls [36]. This lack of significant support, combined with the dangers of BCG [37, 38], has led the AUA to recommend against its use.

The Future of Bladder Instillation Therapy

Beyond the current treatments regimens there are several new and ongoing investigations into other potential intravesicular therapies for IC/BPS. Several of these studies focus on developing more effective strategies for delivering currently available medications. One such treatment is the lidocaine-releasing intravesical system (LiRIS): a device that allows for the continuous release of lidocaine over a period of 2 weeks. Pilot data has been promising: 16 women suffering from ulcerating IC had the device installed via cystoscopy for 14 days at doses of either 200 mg or 650 mg. Both arms tolerated the treatment well, and both demonstrated sustained symptom relief even after the device was removed [20]. The treatment is currently undergoing placebo-controlled clinical trials to assess efficacy [39]. Other ongoing clinical trials for current therapies include research in to the optimal duration of instillation therapy [40], and the development of shelf-stable, premixed instillation cocktails (personal communication). In addition to examining new ways to use current instillation therapies, there is also some investigation into entirely new medications. The most exciting new potential therapy is the use of intravesicular liposomes (LPs). LPs are vesicles composed of concentric phospholipid bilayers separated by aqueous compartments. They create a molecular film when applied to cell walls, and as such it is believed that they restore the GAG layer of bladder epithelium (similar to other instillation therapies). This treatment has been studied in an animal model [41], and pilot data has demonstrated significant improvement in frequency, nocturia, and pain [42]. The drug is currently undergoing a placebo controlled clinical trial to assess efficacy [43].

Our Strategies

For those patients that are referred to our clinic for possible IC/BPS, we follow a four-step protocol (Fig. 1). Patients presenting with pain are first given a lidocaine bladder instillation as a screening tool to differentiate IC/BPS from other possible causes of pelvic pain. Those patients who respond are then given an induction series with a cocktail of 40,000 units heparin intravesicularly (or 200 mg of pentosan polysufate PO), combined with 8–10 mL of lidocaine, and 4–5 mL of sodium bicarbonate (for those patients that cannot tolerate lidocaine, bupivacaine without sodium bicarbonate is substituted). This induction cocktail is based upon thee vidence and suggestions put forth by Parsons [20,40], and has shown good clinical results. Patients are then taught techniques to perform home instillation with this cocktail as mixed by their pharmacist, and can performthese treatments themselves as maintenance therapy. Flare-ups are generally treated with in-office instillations, but can again be treated at home if the patient cannot reach the office or their treating physician is not available..

Compliance with Ethics Guidelines

Conflict of Interest Dr. Marc A. Colaco reported no potential conflicts of interest relevant to this article.

Dr. Robert J. Evans serves on the board of directors for Interstitial Cystitis Assoc. and has received consultancy from Medtronic. Dr. Evans holds stock/stock options in Urigen Pharmaceuticals and has has travel/accommodations expenses covered or reimbursed by Medtronic.

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

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