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Bladder instillation patterns in a cohort of women with interstitial cystitis/bladder pain syndrome

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Abstract

Purpose: To determine intravesical instillation patterns among women receiving treatment for interstitial cystitis/bladder pain syndrome (IC/BPS).

Methods: Using the Veterans Affairs Informatics and Computing Infrastructure, active female users of the Veterans Affairs system with an ICD-9 diagnosis of IC/BPS (595.1) were randomly sampled. Patients were considered to have IC/BPS (by chart review) if they had two visits complaining of bladder-centric pain in the absence of positive urine culture 6 weeks apart or history of bladder pain with one additional visit for bladder-centric pain. We abstracted the dates of intravesical instillations for each patient. A “course” of instillations was defined as 1 instillations made with <21 days between visits.

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Patient consent statement: The Institutional Review Board waived the need to obtain consent for this study as the patient was retrospectively obtained and was made anonymous.

This study did not reproduce material from other sources.

This was an observational study and so no clinical trial registration was obtained.

Ethics of Approval statement: Approval was obtained via the Durham VA Institutional Review Board Durham (VAMC IRB#1936).

Results: We identified 641 women with confirmed diagnosis of IC/BPS, 78 of whom underwent a total of 344 intravesical instillations. On average each subject had 1.5 +/- 0.8 courses between October 2004-July 2016. Each course was an average of 3.1 +/- 2.6 instillations. 55% of courses consisted of one instillation. Only 22% of courses had 6 or more instillations, the number typically recommended to achieve clinical response. Each instillation within a course was an average of 9.4 +/- 4.0 days apart. Most instillations (77%) were a cocktail of two or more drugs.

Conclusions: In our cohort, few women with IC/BPS received a recommended treatment course of six weekly instillations, with most receiving only one per course. Future studies are needed to determine if instillation courses were altered from the guideline due to provider practice patterns, early improvement, or poor tolerance of instillations.

Keywords

Interstitial Cystitis; Intravesical Administration; Pattern

Introduction:

Interstitial cystitis/bladder pain syndrome (IC/BPS) is an enigmatic disorder affecting 197 per 100,000 women and 41 per 100,000 men in the United States.¹ IC/BPS is defined by the International Continence Society as a diagnosis of exclusion that is characterized by persistent or recurrent chronic pain, pressure, or discomfort that appears to be related to the bladder and is accompanied by one or more symptoms such as urgency or frequency.² IC/BPS is a notoriously difficult condition to treat with patients responding differently to various therapies, likely due to different phenotypes of the disorder. There is no set treatment regimen. Instead, the American Urologic Association (AUA) IC/BPS guidelines describe treatment “options” for providers based on limited available evidence.³

Intravesical instillations are described by the AUA as a second-line treatment for IC/BPS.³ Based on the available evidence, reasonable options for intravesical instillation are single or multidose regimens of lidocaine, heparin, and/or dimethyl sulfoxide (DMSO). These agents have shown some efficacy with minimal side effects. A randomized control trial evaluating intravesical instillations of DMSO found that 93% of patients showed improvement compared to 35% of patients who received placebo.⁴ Another trial of patients who underwent 6 weekly instillations of DMSO versus Bacillus Calmette-Guerin (BCG) found that 47% of patients in the DMSO group showed improvement compared to 0% of patients in the BCG group.⁵ Observational studies have similarly found heparin to be efficacious, with 56% of patients reporting clinically significant improvement at 3 months, and 40% reporting continued improvement at 1 year.⁶ A second observational study of patients undergoing biweekly instillations of heparin found that, at 3 months, 72.5% of patients reported significant relief.⁷ Lidocaine was studied in a randomized, multi-center trial which found that, at 15 days, Global Response Assessment scores were significantly improved from placebo, with 66% of patients in the treatment group reporting score improvement versus 42% in the control group.⁸

The guidelines do not provide specific recommendations on timing of treatment or number of treatments.³ Treatments regimens described in the literature differ vastly, with both the

number of instillations and the number of weeks they are performed over differing from study to study. In our experience, providers typically recommend six weekly instillations as an initial course.

We sought to learn more about how IC/BPS treatments are being used in clinical practice by examining data within a national cohort, with this study focusing on the use of intravesical instillations. Instillation patterns vary widely and often do not adhere to AUA or typical provider recommendations; thus, the aim of this study was to provide insight into the typical treatment course. This information can be used to guide clinical decision making with regard to more typical treatment regimens as well as potential more invasive procedures.

Materials and methods:

After obtaining institutional approval (Durham VAMC IRB#1936) the Veterans Affairs Informatics and Computing Infrastructure (VINCI) was queried for all female active users of the Veterans Health Administration (VHA) to identify patients with an ICD-9 diagnosis of IC/BPS (595.1). A random sample of patients was selected, and chart review was performed to confirm that the patients identified truly had IC/BPS. Subjects were required to have two visits complaining of bladder-centric pain in the absence of positive urine culture at least six weeks apart or a history of bladder pain/irritative symptoms with one additional visit complaining of bladder centric pain. These criteria are consistent with the recommended diagnostic criteria of the AUA.³

A cohort of 641 women diagnosed with IC/BPS between October 2004 to July 2016 was identified. Detailed medical record review was performed to determine how many women underwent intravesical instillations and to capture number of courses per patient, number of instillations per course, time between instillations, and medications used in each instillation. Instillations were grouped into “courses”, defined as one or more instillation(s) with 21 days or fewer between instillations.

Codes for the following procedures were used to determine which patients went on to more invasive treatments: InterStim/neuromodulation, cystoscopy with hydrodistension, and cystoscopy with botulinum toxin.

Means of continuous variables were compared using Student’s t-test. Categorical variables were compared using chi-squared analysis. Poisson regression was used to determine the number of instillations per patient, with patient time followed post-diagnosis as an offset. Data are presented as means \pm SD or counts and percent. Analysis performed with SAS v9.3 software.

Results:

Of the 641 women with confirmed diagnosis of IC/BPS, 78 underwent bladder instillations. These 78 women had a mean age of 48.1 \pm 14.6 years and a mean body mass index (BMI) of 29.3 kg/m² \pm 5.5 at the time of diagnosis. Over half (40 patients, 51%) were White, 42% (33 patients) Black, 3% (2 patients) Hispanic, and 4% (3 patients) “Other”. Patients were followed for an average of 67.9 \pm 50.9 months post-IC/BPS diagnosis.

There were a total of 344 instillations in the study period. There were 117 unique courses. On average each subject had 1.5 +/- 0.8 courses over the timeframe analyzed. Fifty patients (64%) had one course, twenty (26%) had two courses, five (6%) had three courses, and three patients (4%) had four courses. Each course was an average of 3.1 +/- 2.6 instillations. Over half (55%) of courses consisted of only one instillation. Only 22% of courses had 6 or more instillations, the number typically recommended to achieve clinical response (Table 1).

Each instillation within a course was an average of 9.4 +/- 4.0 days apart from the prior instillation. Of the 333 instillation visits with complete drug information, 23% utilized only one medication while 77% were a cocktail drug of 2 or more drugs (Table 2). Lidocaine was the most frequent medication used followed by heparin and sodium bicarbonate (Table 3).

Of the 78 patients who received instillations, 18 cases went on to more invasive procedures: four (5.1%) patients received InterStim/neuromodulation, sixteen (21%) received cystoscopy with hydrodistension, and three received cystoscopy with botulinum toxin (3.8%). Average time from final instillation to more invasive procedures was 1288 days +/- 1153. On average, these 18 cases had an average of only 1.7 +/- 0.9 courses of instillations prior to more invasive treatment (Table 4).

Discussion:

We showed that over half of treatment courses in our cohort consisted of only one instillation, with only 22% of courses consisting of six or more instillations. Of the 333 instillation visits with complete drug information, 77% were a cocktail drug of 2 or more drugs. Eighteen patients went on to more invasive treatments.

There are several studies that have compared the different medications used in bladder instillations; however, these papers utilize various instillation regimens.⁸ Examples of the different instillation courses that have been described include both one to three instillations a week for 6 weeks to 12 months and weekly instillations for 8 weeks followed by bi-weekly treatments for 6 months.^{9,10} Jones et al. described regimens for instillation patterns that differed based on the therapy offered.¹¹ They describe lidocaine as being administered weekly for 6 weeks with monthly maintenance, heparin administered 3 times a week for 2-12 weeks with monthly maintenance, dimethyl sulfoxide given weekly for 6-8 weeks with monthly maintenance, and hyaluronic acid, chondroitin sulfate, or pentosan polysulfate sodium given weekly for 4-6 weeks with monthly maintenance.¹¹

This study demonstrated that, in clinical practice within our study population, instillations generally fell within 9 days of each other, similar to what is described in the aforementioned studies. However, courses only consisted of an average of three instillations, with over half of courses consisting of only one instillation, which is fewer than the regimens described in previously published studies. Additionally, these studies focus on the use of one instillation agent at a time, whereas in our study cohort we have found that 77% of instillations were a cocktail of 2 or more drugs.

Interestingly, eighteen of the patients in our study went on to more invasive therapies, including InterStim/neuromodulation, hydrodistension, and cystoscopy with botulinum

toxin. This indicates an instillation treatment failure or possibly undertreatment in these patients. The majority of patients who sought alternative therapies went on to hydrodistension, while a similar number received InterStim/neuromodulation and cystoscopy with botulinum toxin. Neuromodulation has been shown to be an effective treatment following failure of more conservative therapies and prior to major surgery.¹² Cystoscopy with botulinum toxin has also been effective for patients with IC/BPS, but remains a fifth-line therapy.^{3,13} In previous studies, hydrodistension has been less effective long-term; however it remains an alternative option for patients who have failed prior therapies.¹⁴ Each of these studies shows that these more invasive therapies have been effective for patients in some studies.

The study has several limitations. The study population consists of only women, and thus, may not be generalizable to all patients with IC/BPS. The data used in this study would also not be able to account for additional care received outside the VA health care system. Additionally, the drugs used in various courses differed; therefore these results cannot be extrapolated to one specific drug or combination of drugs.

This study is descriptive in nature and interventional studies are recommended to better assess the efficacy of different courses and medications. One of the major strengths of the study is its large population that was examined on a national level. Furthermore, the VHA functions as an HMO, thus most patients within this system receive their care solely through the VA and this reduces the likelihood of missing data.

IC/BPS is a complex condition for which treatment patterns vary widely and do not adhere to typical provider recommendations in the absence of specific regimen guidelines from the AUA. This paper shows that, although previous studies have focused on treatment with one drug and/or treatment regimen, this is not what is being practiced clinically. In actuality, most patients are receiving instillations with two or more drugs, and typical courses consist of an average of 3 instillations, though over half of patients receive only one instillation. Future studies will be needed to investigate the reason behind why the instillation courses were shortened. This may be due solely to provider practice patterns; however, poor tolerance of instillations or early improvement with treatment may also play a role. Standardized treatment regimens would help to determine the impact of these instillation courses. Future study will also be needed to investigate which specific drugs or combinations thereof would be most effective in treatment regimens as well as which next steps in therapy would be most effective.

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Data availability statement:

The data that support the findings of this study are available from the Veterans Health Administration database. Restrictions apply to the availability of these data, which were

used under license for this study. Data are available from the authors with the permission of the Veterans Health Administration.

Abbreviations:

IC/BPS	Interstitial Cystitis/Bladder Pain Syndrome
AUA	American Urological Association
DMSO	Dimethyl Sulfoxide
BCG	Bacillus Calmette-Guerin
VINCI	Veterans Affairs Informatics and Computing Infrastructure
VHA	Veterans Health Administration
BMI	Body Mass Index

References:

1. Clemens JQ, Meenan RT, Rosetti MC, Gao SY, Calhoun EA. Prevalence and incidence of interstitial cystitis in a managed care population. *J Urol.* 2005;173(1):98–102. doi:10.1097/01.ju.0000146114.53828.82 [PubMed: 15592041]
2. Meijlink J. (Ed.). (2018, March). Interstitial cystitis/bladder pain syndrome (IC/BPS). ICS COMMITTEES. Retrieved January 20, 2022, from <https://www.ics.org/committees/standardisation/terminologydiscussions/icbps>
3. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol.* 2011;185(6):2162–2170. doi:10.1016/j.juro.2011.03.064 [PubMed: 21497847]
4. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol.* 1988;140(1):36–39. doi:10.1016/s0022-5347(17)41478-9 [PubMed: 3288775]
5. Peeker R, Haghsheno MA, Holmäng S, Fall M. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. *J Urol.* 2000 Dec;164(6):1912–5; discussion 1915–6. doi: 10.1016/s0022-5347(05)66916-9. [PubMed: 11061879]
6. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol.* 1994 May;73(5):504–7. doi: 10.1111/j.1464-410x.1994.tb07634.x. [PubMed: 8012771]
7. Kuo HC. Urodynamic results of intravesical heparin therapy for women with frequency urgency syndrome and interstitial cystitis. *J Formos Med Assoc.* 2001 May;100(5):309–14. [PubMed: 11432309]
8. Nickel JC, Moldwin R, Lee S, Davis EL, Henry RA, Wyllie MG. Intravesical alkalized lidocaine (PSD597) offers sustained relief from symptoms of interstitial cystitis and painful bladder syndrome. *BJU Int.* 2009 Apr;103(7):910–8. doi: 10.1111/j.1464-410X.2008.08162.x. [PubMed: 19021619]
9. Digesu GA, Tailor V, Bhide AA, Khullar V. The role of bladder instillation in the treatment of bladder pain syndrome: Is intravesical treatment an effective option for patients with bladder pain as well as LUTS?. *Int Urogynecol J.* 2020;31(7):1387–1392. doi:10.1007/s00192-020-04303-7 [PubMed: 32358624]
10. Rössberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side-effects and treatment outcome. *Scand J Urol Nephrol.* 2005;39(1):73–77. doi:10.1080/00365590410018738 [PubMed: 15764276]

11. Jones P, Hjelle KM, Mohn J, Guðbrandsdóttir G, Roth I, Chaudhry AA, et al. Current Status of Intravesical Therapies for Bladder Pain Syndrome (BPS): A Narrative Review of Emerging Evidence. *Urology*. 2021 Oct;156:e48–e57. doi: 10.1016/j.urology.2021.05.042. [PubMed: 34118230]
12. Wang J, Chen Y, Chen J, Zhang G, Wu P. Sacral Neuromodulation for Refractory Bladder Pain Syndrome/Interstitial Cystitis: a Global Systematic Review and Meta-analysis. *Sci Rep*. 2017 Sep 8;7(1):11031. doi: 10.1038/s41598-017-11062-x. [PubMed: 28887515]
13. Chen JL, Kuo HC. Clinical application of intravesical botulinum toxin type A for overactive bladder and interstitial cystitis. *Investig Clin Urol*. 2020 Feb;61(Suppl 1):S33–S42. 10.4111/icu.2020.61.S1.S33
14. Chen Y, Ying Z, Xiao Y, Liu Y, Wu S. The diagnostic and therapeutic efficacy of cystoscopy with hydrodistension and random biopsies in clinically suspected interstitial cystitis/bladder pain syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2021 Oct;265:156–161. doi: 10.1016/j.ejogrb.2021.08.025. Epub 2021 Aug 27. [PubMed: 34492610]

Table 1.

Summary of all courses, including number of instillations per course and what percentage of courses consist of the corresponding number of instillations

Instillations per Course	Number of Courses	Percent of Total
1	64	54.7%
2	8	6.8%
3	3	2.6%
4	6	5.1%
5	10	8.5%
6	19	16.2%
7	0	0.0%
8	2	1.7%
9	1	0.9%
10	2	1.7%
11	2	1.7%

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Table 2.

Breakdown of the number of drugs used per instillation

	Number of instillations	Percentage of instillations
1 drug	77	23%
2 drugs	104	31%
3 drugs	61	18%
4 drugs	52	16%
5 drugs	39	12%
Missing	11	-

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Table 3.

Drugs included in instillations and frequency at which they are used

	N=344 Visits
Lidocaine *	241 (70%)
Heparin *	205 (60%)
SodiumBicarbonate	152 (44%)
DimethylSulfoxide *	129 (38%)
Steroid	57 (17%)
PentosanPolysulfateSodium	45 (13%)
Marcaine	42 (12%)
Missing/Other	11 (3%)

* Instillation agents identified as an option by the American Urological Association IC/BPS Guideline

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Table 4.Number of patients who received 3rd to 5th line alternative therapies

Number of Patients	Intervention
4	InterStim/Neuromodulation
16	Cystoscopy with hydrodistension
3	Cystoscopy with botulinum toxin

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