Received: 26 October 2022 | Accepted: 23 January 2023

DOI: 10.1002/nau.25142

CLINICAL ARTICLE

Neurourology Urodynamics | SUFU | WILEY

A prospective, randomized trial comparing intravesical dimethyl sulfoxide (DMSO) to bupivacaine, triamcinolone, and heparin (BTH), for newly diagnosed interstitial cystitis/painful bladder syndrome (IC/PBS)

Nani P. Moss MD, MPH[1] | Henry H. Chill MD[1] | Peter K. Sand MD[1] | Cecilia Chang MS[2] | Roger P. Goldberg MD, MPH[1] | Adam Gafni-Kane MD[1]

[1]Division of Urogynecology, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, Skokie, Illinois, USA

[2]NorthShore University HealthSystem Research Institute, Evanston, Illinois, USA

Correspondence
Henry H. Chill, MD, Division of Urogynecology, NorthShore University HealthSystem, 9650 Gross Point Rd, Suite 3900, Skokie, IL 60076, USA.
Email: Henchill@gmail.com

Abstract

Introduction and Hypothesis: The primary aim of this study was to compare the effect of bladder instillations using dimethyl sulfoxide (DMSO) with triamcinolone versus bupivacaine, triamcinolone, and heparin (BTH) in women with newly diagnosed interstitial cystitis/painful bladder syndrome. The primary outcome was improvement in symptoms measured using the O'Leary-Sant Interstitial Cystitis Symptoms Index (ICSI) score. Secondary comparisons included changes in urinary frequency, nocturia, and bladder capacity.

Materials and Methods: This was a prospective, randomized study. Patients with a recent diagnosis of interstitial cystitis/painful bladder syndrome (IC/PBS) were randomized 1:1 to treatment with either 6 weekly bladder instillations of DMSO with triamcinolone or BTH. During follow-up visits, patients completed the ICSI questionnaire, and bladder capacity was determined through the retrograde filling of the bladder. The χ^2 test or Student's t test were used for data analysis.

Results: A total of 83 patients were randomized, and final analysis included 70 participants who completed the 6 weekly instillations (42 DMSO, 28 BTH). The groups were similar in baseline demographics and clinical characteristics, except for cystometric maximum capacity (DMSO 338.62± 139.44 mL, BTH 447.43 ± 180.38 mL, $p = 0.01$). In the DMSO group, 63% of patients had a greater than 29.5% reduction in total ICSI score versus 43% in the BTH group ($p = 0.15$). Nocturia and pain were significantly reduced in the DMSO group. There was a significant increase from baseline in bladder capacity for both groups.

Nani P. Moss and Henry H. Chill contributed equally to this study.

Conclusion: In women with newly diagnosed IC/PBS, bladder instillations with DMSO and triamcinolone provide greater improvement in pain and nocturia compared to BTH.

KEYWORDS
bladder instillations, dimethyl sulfoxide (DMSO), interstitial cystitis, intravesical instillation, painful bladder syndrome

1 | INTRODUCTION

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a debilitating condition characterized by urinary urgency, frequency, nocturia, and pain, without evidence of urinary tract infection or other identifiable causes.[1–3] The exact etiology of IC/BPS is unknown, but several hypotheses have been proposed, all of which contribute to urothelial, vascular, and neurologic damage, followed by irritating voiding symptoms and pain.[4] Therapy is generally limited to symptom relief[3,5] with limited high-quality data on the efficacy of specific treatment options.

Several intravesical treatment regimens for IC/PBS have been described in the literature. Intravesical instillation treatment with dimethyl sulfoxide (DMSO) is a Food and Drug Administration-approved treatment for IC/PBS. At our institution, we have found success with the use of an intravesical mixture of bupivacaine, triamcinolone, and heparin (BTH) as an alternative to DMSO. While this regimen itself has not been formally studied, the intravesical application of each component has been described in the literature.[6–12] Additionally, data on objective measures of response for treatment with DMSO is limited. One recent randomized, double-blind, placebo-controlled study, found that an intravesical solution of KRP-116D (50% DMSO) improved symptoms and voiding parameters.[13] As reduction in bladder capacity is often observed in patients with IC/PBS,[14] using it to measure objective improvement seems relevant.

The primary aim of this study was to determine whether bladder instillations using DMSO with triamcinolone or BTH would lead to significant improvement in symptoms measured using the O'Leary-Sant Interstitial Cystitis Symptoms Index (ICSI) score in women with newly diagnosed IC/PBS. Secondary comparisons included changes in urinary frequency, nocturia, and pain, as determined from individual questions from the ICSI, along with bladder capacity.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a prospective, randomized, non-blinded study, performed at a university-affiliated urogynecology division between October 2011 and April 2019. Approval for the study was received from the NorthShore University HealthSystem Institutional Review Board (EH11-081). Inclusion criteria included patients 18 years of age or older with newly diagnosed IC/PBS who chose to undergo treatment with bladder instillations. Subjects were diagnosed on a clinical basis as defined by the International Continence Society having suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary tract infection or other obvious pathology.[15] Excluded were patients with a history of pelvic radiation, bladder malignancy, or bladder resection as they may demonstrate reduced bladder capacities due to decreased bladder compliance and size. Patients were required to refrain from the use of concomitant pain medications during the study. All patients were encouraged to follow a diet aimed at reducing bladder irritation.

2.2 | Study procedures

Once written informed consent to participate was obtained, study participants were randomized 1:1 to one of two intervention groups: (1) Treatment with bladder instillations of DMSO with triamcinolone (DMSO group); (2) bladder instillation with BTH (BTH group). Treatment for both groups included 6 weekly sessions. Method of randomization included a computer-generated random number table created before the start of the study.

During weekly visits, bladder capacity was determined, after which patients were treated with the instillation of either DMSO with triamcinolone or BTH. Sterile water was used to retrograde fill the

bladder through a catheter. The volume at which each patient stated she can no longer tolerate further instillation of fluid was recorded and defined as the bladder capacity. Patients were asked to hold this amount for 5 min, then their bladders were emptied with a catheter. The bladder was then reinstilled with either 50 mL of DMSO and 1 mL of triamcinolone (10 mg/mL) or 30 mL of 0.5% bupivacaine (5 mg/mL), 2 mL triamcinolone (10 mg/mL), and 2 mL heparin (10 000 units/mL). Participants were instructed to hold the instillation in their bladder for 15 min, then to empty their bladder by voiding. They received a single dose of a prophylactic antibiotic, either nitrofurantoin or sulfamethoxazole/trimethoprim, depending on allergies, before leaving.

2.3 | Outcome measures

Patients completed the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI)[16] at each of their six treatment visits. The ICSI is a validated questionnaire designed to capture the most important voiding and pain symptoms associated with IC/PBS, and it consists of four questions addressing symptoms of urgency of urination, frequency of urination, nighttime voids, and pain or burning in the bladder. The questions are scored from 0 (not at all) to 5 (almost always), with a maximum score of 20.

Our primary outcome was defined as the percentage of patients who experienced a greater than 29.5% reduction in ICSI score following treatment. Secondary outcomes included change in bladder capacity and urinary symptoms including frequency, nocturia, and pain, as determined from individual questions from the ICSI questionnaire.

To determine sample size, previously published studies on IC/PBS treatments were used. A study by Lubeck et al. determined that a reduction of at least 29.5% in ICSI score following treatment for bladder pain corresponded with moderate to marked improvement in symptoms on the Patient Overall Rating of Improvement of Symptoms Index.[17] Using global assessments of response, Perez-Marrero found that intravesical treatment with DMSO evoked a moderate improvement in 40% of patients.[18] Nomiya et al. reported a moderate response in 15% of patients treated with lidocaine and heparin instillations.[19] Using 80% power, a significance threshold of 0.05 and relying on the previous data mentioned, 49 subjects per group would enable the detection of a 25% difference in treatment response.

2.4 | Statistical analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc.). Baseline demographics, clinical characteristics, measurements obtained at visit six, and changes in ICSI score and bladder capacity at each visit, were compared between subjects receiving DMSO and BTH using Student's t test or χ^2 test. Changes in subjective complaints of symptoms associated with IC/PBS, as determined by the ICSI, between study groups and across visits (at visits 1, 5, and 6), were compared and assessed by mixed-effects models. Statistical significance was established at $p < 0.05$.

3 | RESULTS

A total of 83 patients were randomized for the study. Final analysis included 70 participants who completed the 6 weekly instillations; 42 received DMSO with triamcinolone, and 28 were treated with BTH. The two groups were generally similar in baseline demographic and clinical data, as well as baseline scores on questionnaires (Table 1). The DMSO group had a smaller mean cystometric bladder capacity compared to the BTH group (338.62 ± 139.44 vs. 447.43 ± 180.38 mL, $p = 0.01$). All other baseline characteristics were similar between groups.

For our primary outcome, 63% of patients in the DMSO group versus 43% in the BTH group had a greater than 29.5% reduction in total ICSI score at visit 6 ($p = 0.15$) (Table 2). At each instillation visit, ICSI scores decreased in both treatment groups (Table 3). However, there was a significant difference in the change of total ICSI score for patients in the DMSO group at visits 5 (-4.47 ± 3.56) and 6 (-4.73 ± 4.15) when compared to the BTH group (-2.18 ± 3.11 for visit 5 and -2.24 ± 2.72 for visit 6, $p = 0.02$ each) (Table 3).

In examining the individual questions in the ICSI, symptoms of urgency and frequency improved significantly for both treatment groups ($p < 0.01$). The number of nighttime voids was significantly improved in the DMSO group, where mean score of the ICSI on nighttime voids decreased from 2.33 ± 1.41 to 1.56 ± 1.19 at visit 6 ($p < 0.01$), while no change in nighttime voids was reported in the BTH group ($p = 0.7$). Pain was significantly improved overall in those receiving DMSO treatment ($p < 0.01$), but this was not observed in the BTH study participants ($p = 0.07$). At visits 5 and 6, the DMSO group had significantly improved pain when compared to the BTH group ($p = 0.03$ and $p = 0.01$, respectively) (Table 4).

TABLE 1 Baseline demographics and clinical characteristics.

Characteristic	DMSO	BTH	*p* Value
Age—years	46.38 ± 17.83	51.36 ± 12.25	0.17
Body mass index	27.97 ± 12.95	28.02 ± 8.29	0.99
Duration of symptoms—months	32.77 ± 65.51	26.32 ± 23.26	0.67
Sexually active—no./total no. (%)	26/34 (76.47)	16/25 (64)	0.30
Post-menopausal—no./total no. (%)	15/40 (37.5)	15/27 (55.56)	0.14
Cystometric testing: first sensation—mL	129.24 ± 81.65	117.62 ± 72.23	0.60
Cystometric testing: fullness—mL	226.62 ± 106.91	260 ± 93.87	0.23
Cystometric testing: maximum capacity—mL	338.62 ± 139.44	447.43 ± 180.38	0.01
Detrusor overactivity—no./total no. (%)	12/31 (38.71)	12/24 (50.0)	0.4
Retrofill volume—mL	170.37 ± 76.08	209.07 ± 110.90	0.12
Frequency—h	1.86 ± 0.98	2.12 ± 1.25	0.35
Nocturia—number of voids	3.02 ± 1.90	3.00 ± 2.90	0.97
ICSI—score	10.65 ± 3.90	9.48 ± 4.68	0.3

Note: Data presented as mean ± SD or *N* (%).

Abbreviations: BTH, bupivacaine triamcinolone heparin; DMSO, dimethyl sulfoxide; ICSI, O'Leary-Sant Interstitial Cystitis Symptoms Index.

TABLE 2 Clinical characteristics at visit 6.

	DMSO		BTH		
	n	% or mean ± SD	*n*	% or mean ± SD	*p* Value
Retrofill volume—mL	38	263.42 ± 114.21	23	288.26 ± 102.94	0.4
Frequency—h	38	2.82 ± 1.24	23	3.22 ± 1.12	0.22
Nocturia—number of voids	38	1.74 ± 1.76	22	2.27 ± 2.10	0.29
ICSI—score	30	5.57 ± 3.55	22	7.00 ± 4.23	0.19
<29.5% reduction from visit 1	11	36.67	12	57.14	0.15
≥29.5% reduction from visit 1	19	63.33	9	42.86	

Abbreviations: DMSO, dimethyl sulfoxide; BTH, bupivacaine triamcinolone heparin; ICSI, O'Leary-Sant Interstitial Cystitis Symptoms Index.

TABLE 3 Changes in ICSI compared to visit 1.

	DMSO		BTH		
	n	Mean ICSI score ± SD	*n*	Mean ICSI score ± SD	*p* Value
Visit 2	32	−0.91 ± 2.39	23	−0.61 ± 2.10	0.63
Visit 3	32	−2.34 ± 2.36	25	−1.72 ± 3.10	0.39
Visit 4	33	−3.24 ± 3.24	23	−2.83 ± 3.38	0.64
Visit 5	32	−4.47 ± 3.56	22	−2.18 ± 3.11	0.02
Visit 6	30	−4.73 ± 4.15	21	−.24 ± 2.72	0.02

Abbreviations: BTH, bupivacaine triamcinolone heparin; DMSO, dimethyl sulfoxide; ICSI, O'Leary-Sant Interstitial Cystitis Symptoms Index.

An increase in bladder capacity from baseline was noted for both treatment groups, as measured from retrofill volumes before instillations (Table 5). After the first instillation, the DMSO group increased bladder capacity by 49± 65 mL with a percent increase of change of 32.65 ± 35.88%, which was statistically significant when compared to the increased bladder volume (18 ± 30 mL, $p = 0.01$) and percent increase of the BTH group (13.15 ± 18.41%, $p < 0.01$). There were no other statistically significant increases in retrofill bladder volumes or percent increase in bladder capacity between the two groups. However, the DMSO group's bladder capacity increased by 97 ± 100 mL after the 6 weeks of treatment, while the BTH group increased bladder capacity by 67 ± 75 mL ($p = 0.23$). This translated to a 74% increase in bladder capacity in the DMSO group, with a corresponding 46% increase in those receiving BTH ($p = 0.16$).

Of the 13 patients who were randomized, but either withdrew consent from or were ineligible to participate, 5 were randomized to DMSO with triamcinolone and 8 to BTH. Two participants in the BTH group were screening failures (on Elmiron). Three withdrew due to discomfort experienced during the instillation, two from the DMSO group and one from BTH. One participant developed urinary tract infections after treatments, despite antibiotic prophylaxis, and she stopped receiving instillations after the third session. Two patients randomized to BTH and one participant to DMSO with triamcinolone were unable to make the weekly visits. Two participants in the DMSO group ultimately desired to choose their instillation type. Finally, one participant randomized to receive BTH withdrew from the study as she was concerned about the chemical composition of DMSO.

TABLE 4 ICSI of individual questions compared to visit 1.

	DMSO		BTH		
	n	**Mean ± SD**	***n***	**Mean ± SD**	***p* Value**
How often have you felt a strong need to urinate with little or no warning?					
Visit 1	27	2.63 ± 1.57	15	1.87 ± 1.55	0.14
Visit 5	26	1.46 ± 1.03	15	1.27 ± 1.33	0.06
Visit 6	25	1.24 ± 1.01	15	1.07 ± 1.22	0.63
p Value	<0.01		<0.01		
Have you had to urinate less than 2 h after you finished urinating?					
Visit 1	27	3.48 ± 1.53	15	2.67 ± 1.59	0.11
Visit 5	26	1.88 ± 1.53	15	1.87 ± 1.60	0.97
Visit 6	25	1.76 ± 1.20	15	2.00 ± 1.56	0.59
p Value	<0.01		<0.01		
How often do you most typically get up at night to urinate?					
Visit 1	27	2.33 ± 1.41	15	2.07 ± 1.39	0.11
Visit 5	26	1.42 ± 1.27	15	2.20 ± 1.42	0.08
Visit 6	25	1.56 ± 1.19	15	2.13 ± 1.51	0.19
p Value	<0.01		0.70		
Have you experienced pain or burning in your bladder?					
Visit 1	27	1.89 ± 1.34	15	2.40 ± 1.55	0.27
Visit 5	26	0.96 ± 0.82	15	1.93 ± 1.49	0.03
Visit 6	25	0.76 ± 0.66	15	1.80 ± 1.37	0.01
p Value	<0.01		0.07		

Abbreviations: DMSO, dimethyl sulfoxide; BTH, bupivacaine triamcinolone heparin; DMSO, dimethyl sulfoxide; ICSI, O'Leary-Sant Interstitial Cystitis Symptoms Index.

TABLE 5 Retrofill volume change (mL) compared to baseline volume.

	DMSO		BTH		
	n	**Mean ± SD**	***n***	**Mean ± SD**	***p* Value**
Visit 2	39	49.23 ± 65.07	27	18.15 ± 30.04	0.01
Visit 3	40	59.00 ± 59.09	27	34.33 ± 60.33	0.10
Visit 4	40	74.63 ± 67.47	26	56.73 ± 48.83	0.25
Visit 5	39	90.00 ± 78.88	24	55.63 ± 61.76	0.07
Visit 6	38	96.71 ± 99.88	22	66.59 + 75.30	0.23

Abbreviations: BTH, bupivacaine triamcinolone heparin; DMSO, dimethyl sulfoxide.

4 | DISCUSSION

Our study is the first to apply a prospective randomized study design to compare DMSO with triamcinolone and BTH bladder instillations for the treatment of symptoms of IC/PBS. We found a clear advantage in using DMSO with triamcinolone compared to BTH. While both treatment modalities provided overall symptomatic relief, as measured by decreases in scores on the ICSI, patients treated with DMSO and triamcinolone had decreased nighttime voids and pain compared to those treated with BTH. This study is generalizable to subspecialty urogynecology practices that treat IC/PBS.

The DMSO group had more symptomatic relief of their IC/PBS based on scores on the ICSI, with 63% of participants achieving the clinically significant threshold set by us during study design. Only 43% of study participants in the BTH group reported this change. While this difference did not reach statistical significance, it shows a clear trend in favor of bladder instillations with DMSO and triamcinolone compared

to BTH. These results may have been affected by our sample size, which if increased may have resulted in a statistically significant advantage for treatment with DMSO.

Both treatment groups had a decrease in ICSI scores at each visit. There was a statistically significant change from baseline scores in the DMSO group, which was observed at visits five and six compared to the BTH group. This is helpful in counseling patients that after four instillations with DMSO and triamcinolone, they are likely to see a significant improvement in their IC/PBS symptoms and can help set expectations for the course of treatment. In addition, pain, as explored in the ICSI questionnaire, was improved at visits five and six, also only seen in the DMSO group.

Our findings of the clinical efficacy of DMSO and BTH are in accordance with previous studies. One study evaluated DMSO every 2 weeks for four sessions compared to placebo with the primary outcome being 50% improvement in bladder capacity 1 month after treatment. In the DMSO group, 93% of patients improved compared to 35% in the placebo group.[18] In another randomized controlled study, Peeker et al. compared DMSO to bacillus Calmette–Geurin (BCG) instillations. Patients treated with DMSO were found to have reduction in bladder pain compared to the BCG group.[20] In one notable prospective, double-blind, crossover trial, Parsons et al. compared a mixture of heparin and bupivacaine to placebo. Within the treatment group, 50% of patients had decreased frequency and urgency and 42% had reduced pain compared to controls.[21]

Data comparing instillations with DMSO versus BTH is scarce. In one retrospective study conducted by our group, 46 patients receiving DMSO instillations were compared to 146 patients treated with BTH. Improvement in symptoms compared to baseline was reported for both treatment regimens. Direct comparison revealed patients treated with DMSO had greater percentage of overall improvement ($p = 0.02$). Furthermore, patients treated with DMSO experienced a significant decrease in nocturia episodes when compared to those treated with BTH ($p = 0.02$).[22] In our current study, we found number of nighttime voids and pain were reduced in the DMSO group compared to the BTH group. We further found a trend in favor of the DMSO group with regard to symptoms relief evaluated by ICSI scores. This suggests DMSO is superior to BTH when treating patients with IC/PBS.

Change in bladder capacity following intravesical therapy for treating IC/PBS has been investigated, but this is the first study to perform a formal statistical analysis, using it to determine efficacy of treatment. At baseline, the two groups were not different in terms of retrofill bladder capacity, but the mean cystometric maximum capacity for the DMSO group was smaller. Bladder capacity increased from baseline for both treatment groups, as measured from retrofill volumes before instillations. The smaller bladder capacity at starting point in the DMSO group and the equivalent bladder capacity in both groups following the last visit suggest an advantage in using DMSO with triamcinolone compared to BTH, though this is a point in need of further study.

Anecdotally, it is often thought that patients treated with intravesical DMSO experience more pain in comparison to those being treated with BTH, and this dissuades providers from offering DMSO to those with more severe symptoms. Hung et al. reported a dropout rate of 6.7% in patients receiving bladder instillations with DMSO attributed to bladder irritation.[23] In another more recent study, patients were allocated to receive either bladder instillation with KRP-116D (50% DMSO solution) versus placebo. Bladder discomfort (8.2% vs. 2.1%), irritation (10.2% vs. 2.1%), and pain (30.6% vs. 20.1%) were increased in the DMSO group compared to patients who received placebo.[13] In our current study, three participants withdrew due to discomfort experienced during the instillations, two from the DMSO group and one from BTH. These data provide evidence that the majority of patients are able to tolerate instillations with either medication and that the discomfort experienced during DMSO treatments was not so overwhelming as to lead to treatment cessation. In fact, this study provides support that DMSO is more likely to reduce patient pain symptoms. In our clinical experience, instilling triamcinolone with DMSO may decrease instillation-related inflammation leading to reduced patient discomfort and increased tolerability. Furthermore, we believe that a clear discussion about the risk for an initial pain flare with DMSO but an overall improvement in pain, mitigates distress over the occurrence of pain flares.

There are several limitations to this study. A placebo-controlled trial was not performed, as we felt patients should receive an active agent for their painful symptoms rather than placebo. A double-blinded trial was challenging due to the characteristic strong odor of DMSO. A cross-over study was not performed as the effect of initial randomization to either DMSO or BTH may be reflected in bladder capacity measurements once a patient crossed over to the other therapy. We did not meet our predetermined sample size of 49 participants per group. Despite this, there were statistically significant differences between

the two treatment modalities. The randomization process was also a limitation, as randomization of our subjects was done by random number generator. This can lead to an imbalance in treatment assignments if sample size is not met. Data regarding the presence of Hunner's ulcers during pretreatment cystoscopy was unavailable. Finally, during the study, participants were asked to refrain from the use of concomitant pain medications during the study, and all patients were encouraged to follow a diet aimed at reducing bladder irritation. However, no data was collected regarding each patient's specific diet.

In conclusion, in patients with newly diagnosed IC/PBS, bladder instillations using DMSO with triamcinolone provide greater symptom improvement compared to BTH. The full effect of these therapies emerged only after four sessions of once-weekly therapy. Further research is needed to examine the longer-term success of intravesical therapy, and to determine if there is a specific type of patient who is more likely to benefit from a given therapy.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data for this study is available upon request from the corresponding author.

ETHICS STATEMENT

IRB approval was received for this study (EH11-081). All patients participating in the study consented to their participation.

ORCID

Henry H. Chill https://orcid.org/0000-0002-2668-1612
Peter K. Sand http://orcid.org/0000-0002-6946-2524

REFERENCES

1. Konkle KS, Berry SH, Elliott MN, et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND interstitial cystitis epidemiology study. *J Urol*. 2012;187(2):508-512.
2. 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.
3. Peters K, Diokno A, Steinert B, et al. The efficacy of intravesical tice strain bacillus Calmette-Guerin in the treatment of interstitial cystitis: a double-blind, prospective, placebo controlled trial. *J Urol*. 1997;157(6):2090-2094.
4. Hanno PM. Bladder pain syndrome (interstitial cystitis) and related disorder. In: Hanno PM, Wein AJ, Kavoussi LR, Partin AW, Peters C, eds. *Campbell–Walsh Urology Inc*. 11th. Elsevier; 2016:334-370.
5. Propert KJ, Payne C, Kusek JW, Nyberg LM. Pitfalls in the design of clinical trials for interstitial cystitis. *Urology*. 2002;60(5):742-748.
6. Welk BK and Teichman JMH. Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. *Urology*. 2008;71(1):67-70.
7. Parsons CL. Successful downregulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. *Urology*. 2005;65(1):45-48.
8. McInerney PD, Grant A, Chawla J, Stephenson TP. The effect of intravesical Marcain instillation on hyperreflexic detrusor contractions. *Paraplegia*. 1992;30(2):127-130.
9. Matthews RD, Nolan JF, Libby-Straw JA, Sands JP. Transurethral surgery using intravesical bupivacaine and intravenous sedation. *J Urol*. 1992;148(5):1475-1476.
10. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol*. 1994;73:504-507.
11. Perez-Marrero R, Emerson LE, Maharajh DO, Juma S. Prolongation of response to DMSO by heparin maintenance. *Urology*. 1993;41(suppl 1):64-66.
12. Cox M, Klutke JJ, Klutke CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. *Can J Urol*. 2009;16(2):4536-4540.
13. Yoshimura N, Homma Y, Tomoe H, et al. Efficacy and safety of intravesical instillation of KRP-116D (50% dimethyl sulfoxide solution) for interstitial cystitis/bladder pain syndrome in Japanese patients: a multicenter, randomized, double-blind, placebo-controlled, clinical study. *Int J Urol*. 2021;28(5):545-553.
14. Perez-Marrero R, Emerson L, Juma S. Urodynamic studies in interstitial cystitis. *Urology*. 1987;29(4):27-30.
15. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. *Urology*. 2003;61(1):37-49.
16. O'Leary MP, Sant GR, Fowler FJ, Whitmore KE, Spolarich-Kroll J. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(5A suppl):58-63.
17. Lubeck DP, Whitmore K, Sant GR, Alvarez-Horine S, Lai C. Psychometric validation of the O'Leary-Sant Interstitial Cystitis Symptom Index in a clinical trial of pentosan polysulfate sodium. *Urology*. 2001;57(suppl 6):62-66.
18. Perez-Marrero R, Emerson LE, Feltis JT. A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol*. 1988;140(1):36-39.
19. Nomiya A, Naruse T, Niimi A, et al. On- and post-treatment symptom relief by repeated instillations of heparin and alkalized lidocaine in interstitial cystitis. *Int J Urol*. 2013;20(11):1118-1122.
20. Peeker R, Haghsheno MA, Holmang S, Fall M. Intravesical bacillus calmette-geurin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective randomized double-blind study. *J Urol*. 2000;164:1912-1916.

21. Parsons CL, Zupkas P, Proctor J, et al. Alkalinized lidocaine and heparin provide immediate relief of pain and urgency in patients with interstitial cystitis. *J Sex Med*. 2012;9(1):207-212.
22. Iyer S, Lotsof E, Zhou Y, et al. Which bladder instillations are more effective? DMSO vs. bupivacaine/heparin/triamcinolone: a retrospective study. *Int Urogynecol J*. 2017;28(9):1335-1340.
23. Hung MJ, Chen YT, Shen PS, Hsu ST, Chen GD, Ho ESC. Risk factors that affect the treatment of interstitial cystitis using intravesical therapy with a dimethyl sulfoxide cocktail. *Int Urogynecol J*. 2012;23:1533-1539.

How to cite this article: Moss NP, Chill HH, Sand PK, Chang C, Goldberg RP, Gafni-Kane A. A prospective, randomized trial comparing intravesical dimethyl sulfoxide (DMSO) to bupivacaine, triamcinolone, and heparin (BTH), for newly diagnosed interstitial cystitis/painful bladder syndrome (IC/PBS). *Neurourol Urodyn*. 2023;1-8. doi:10.1002/nau.25142