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ORIGINAL ARTICLE

Which bladder instillations are more effective? DMSO vs. bupivacaine/heparin/triamcinolone: a retrospective study

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Abstract
Introduction and hypothesis Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic and debilitating condition. Our objective was to compare two different bladder instillation treatments in patients with BPS/IC: dimethyl sulfoxide with triamcinolone (DMSO) vs. bupivacaine with heparin and triamcinolone (B/H/T). Our hypothesis was that both treatments are equally effective.
Methods A retrospective cohort study of instillation-naïve patients was conducted comparing responses to either DMSO or B/H/T at our tertiary urogynecology center from 2012 to 2014. The primary outcome was patient-reported percent of overall improvement from baseline. Secondary outcomes were change in patient-reported daytime voiding frequency (hours) and change in number of nighttime voiding episodes. Variables analyzed as potential confounders included pelvic pain, cystoscopy findings, levator spasm, and fibromyalgia. The two-sided Student's *t* test, chi-squared test, Poisson regression, and repeated-measure analysis of variance (ANOVA) were used for analyses.
Results One hundred and ninety-three eligible patients were identified (45 receiving DMSO, 146 receiving B/H/T). Compared with baseline, DMSO patients reported 63% improvement ($p < 0.0001$), increased time between daytime voids by 1.5 h ($p < 0.00$), and a 40% reduction in nocturia episodes ($p < 0.00$). B/H/T patients reported 51% improvement ($p < 0.00$), increased time between daytime voids by 1.4 h ($p < 0.00$), and an 8% reduction in nocturia episodes ($p = 0.26$). When comparing the two treatments, DMSO resulted in a greater percentage of overall improvement ($p = 0.02$) and a significant decrease in nocturia episodes when compared with B/H/T ($p = 0.02$). There was no significant difference between treatments for daytime voiding frequency ($p = 0.50$).
Conclusion Bladder instillations with DMSO or B/H/T provide overall symptomatic improvement and improved frequency and nocturia. DMSO appears to provide greater improvement in nocturia and overall.

Keywords Interstitial cystitis · Bladder instillations · Treatment

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a debilitating chronic condition characterized by common clinical symptoms of urinary urgency, pain with urinary voiding, nocturia, and urinary frequency [1]. BPS/IC more commonly occurs in women and is often diagnosed after referral to a urogynecologist or urologist. These symptoms often disrupt sleep, work, and the social life patients.

Treatment options are targeted toward pain control and improving symptoms. The American Urological Society (AUA) recommends conservative treatment, such as patient education, attention to dietary triggers, and stress management, as first-line therapies [2]. Second-line treatments

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include pelvic floor physical therapy aimed at muscle relaxation; medications such as amitriptyline, cimetidine, hydroxyzine, or pentosan polysulfate; and bladder instillations with dimethyl sulfoxide (DMSO), heparin, or lidocaine. Third-line treatments include cystoscopy with hydrodistention, and fourth-line treatments include insertion of a sacral neuromodulator device [2]. Controversy exists surrounding the type and duration of bladder instillations used to alleviate symptoms. There are studies that evaluate the outcomes of a single instillation regimen and comparisons between treatment regimens but none that compare two current AUA-recommended treatment regimens.

We sought to compare clinical outcomes in patients being treated for BPS/IC with DMSO plus triamcinolone compared with a mixture of bupivacaine, heparin, and triamcinolone (B/H/T). These treatment regimens are commonly used for bladder instillations and are used in our center. Our primary objective was to compare DMSO and B/H/T bladder instillation treatments to determine if one was more efficacious than the other at improving overall patient-reported improvement. Our secondary objective was to compare hours between daytime voids and nocturia between groups. Our hypothesis was that both treatments are equally effective.

Materials and methods

We conducted a retrospective cohort study comparing outcomes for patients receiving bladder instillations with DMSO or B/H/T for BPS/IC at our tertiary Female Pelvic Medicine and Reconstructive Surgery (FPMRS) Center between 1 January 2012 and 1 January 2015. The initial data set was obtained from the electronic database using an *International Classification of Diseases*, 9th edn. (ICD9) code of 595.1 for interstitial cystitis and bladder pain syndrome and a CPT code of 51700 for bladder instillations. All instillation-naïve patients who underwent bladder instillation treatment with the diagnosis of BPS/IC were included. Charts were excluded if patients changed instillation therapy type during their course. All other charts were included. IRB approval was obtained from North Shore University Health System (EH15-187).

When patients present to our outpatient urogynecology practice, they are diagnosed with IC/PBS by clinical history and physical exam. As part of their workup, they may or may not have a cystoscopy. All patients are initially offered a trial of conservative behavioral therapy and dietary changes. When patients fail conservative therapy, they are primarily offered physical therapy or bladder instillations. If they choose bladder instillations, they return for 6 weekly instillations with a trained FPMRS nurse who records patient-reported percentage of improvement, daytime urinary frequency, and nocturia at each visit. After the six treatments, patients are evaluated by a physician and their overall treatment outcome assessed.

For DMSO instillations, patients are asked to void and then are catheterized to ensure that their bladder is empty prior to instillation therapy. Their bladder is then instilled with a mixture of 50 ml DMSO (54 g) with 1 ml triamcinolone (10 mg). Patients are asked to hold the instillation for 15 min and void again on their own prior to leaving the office. For B/H/T instillations, patients also are asked to void and are catheterized to ensure their bladder is empty prior to instillation therapy. Then, their bladder is instilled with a mixture of 30 ml of 0.5% bupivacaine (concentration of 5 mg/ml), 2 ml of triamcinolone (20 mg at a concentration of 10 mg/ml), and 2 ml of heparin (20,000 U at a concentration of 50,000 U/5 ml). Patients are asked to hold the instillation medication as long as they can or up to 4 h prior to voiding.

Variables extracted from the chart review included baseline characteristics of gravity, parity, urinary frequency, nocturia, levator spasm, history of fibromyalgia, pelvic pain, pelvic pressure, prior pelvic floor physical therapy, prior treatment for overactive bladder (OAB) with medications, behavioral or other therapy, and prior treatment for BPS/IC with Elmiron. Baseline characteristics were based on previous literature or clinical impression of factors thought to influence treatment results. If patients had a cystoscopy as part of their initial workup, findings were recorded. The primary outcome is difference in subjective overall percent improvement from baseline to after installation treatment (ranging from 1 to 6 sessions) between treatment groups. At each instillation and the follow-up visit, the nurse and doctor, respectively, ask: "How improved from your baseline are you since your last visit?" (pain and urinary urgency; frequency). Patients reported improvement as a percentage (0–100%). Secondary outcomes included change in daytime voiding frequency (hours) and number of nighttime voiding episodes (nocturia) from baseline between groups, as well as time to retreatment. Because of the retrospective nature of the study, only data recorded in the patients' chart could be obtained.

An a priori sample size and power calculation was performed based on improvement seen with DMSO treatment in the retrospective study by Gafni-Kane et al. of 45% subjective improvement [3]. Welk and Teichman treated 23 patients with a mixture of lidocaine, bicarbonate, and heparin and noted that 65% of patients reported >50% improvement on the Patient Objective Rating of Improvement of Symptom scale [4]. Because there are no trials comparing DMSO to B/H/T, a significant clinical difference of 20% was used for the power calculation. A sample size of 310 was needed to have a power of 80% to detect a 20% difference in percentage improvement rates between the two treatment groups, with a 0.5% alpha. Based on chart review conducted prior to the study, we predicted a 4:1 ratio of B/H/T to DMSO and based the above calculation on this ratio. After reviewing our data, we found

a 3:1 ratio of B/H/T to DMSO ratio. This new ratio enabled us to recalculate a smaller sample size of 220. In our review, we found only 193 patients who underwent bladder instillation treatment, and two patients were excluded because they received both instillation therapies at the same time. We did not meet our power calculation but found significance in our data analysis despite this.

Summary descriptive statistics were calculated as mean [standard deviation (SD)] and median (range) for continuous variables, and *N* (%) for categorical variables. Continuous variables were compared between groups T using two-sample *t* test or Wilcoxon rank-sum test. Categorical variables were compared using chi-squared or Fisher's exact test. Repeated-measure Poisson regression was used to analyze daytime voiding and nocturia frequencies for within- and between-group change. Percentage improvement and nocturia frequency were analyzed using repeated measure analysis of variance (ANOVA) for both within- and between-group comparisons. Pearson correlation coefficients were calculated with *p* values to show the direction and strength of association for percentage improvement, changes in daytime voiding frequency, and nocturia.

Results

One hundred and ninety-three patient charts meeting inclusion criteria were identified. Two charts were excluded because the patients changed instillation medication multiple times during their course of treatment. The records of 191 patients undergoing their first series of bladder instillations with DMSO or B/H/T were reviewed. Forty-five patients received DMSO instillations and 146 patients received B/H/T. Baseline patient characteristics are presented in Table 1, with no significant differences between groups, except frequency and nocturia. Patients undergoing instillations with DMSO had increased daytime voiding frequency (1.8 h) compared with B/H/T (2.2 h) ($p = 0.04$). Patients undergoing DMSO instillations also had increased nocturia, voiding on average 2.73 times per night compared with 2.13 times per night for B/H/T ($p = 0.01$). There were no reported adverse reactions to either instillation treatment. Please see Fig. 1 for patient inclusion and retreatment.

Primary outcome: percentage overall symptom improvement

The primary outcome was a comparison of the overall subjective percentage improvement rate during treatment between groups. Both DMSO and B/H/T groups had significant self-reported improvement, with the DMSO having a mean of 63% improvement from baseline ($p < 0.00$) and B/H/T reporting 51% ($p < 0.00$). When comparing groups, patients who received DMSO had significantly higher reported percentage improvement compared with the B/H/T group ($p = 0.02$) (Table 2).

A Pearson correlation was determined for urinary frequency and nocturia from patient-reported percentage improvement. When a patient reported less frequent daytime voids, they also reported greater overall improvement in symptoms (correlation coefficient 0.1–0.5). For patients undergoing DMSO treatment, as their time interval between daytime

Table 1 Comparison of baseline characteristics between dimethyl sulfoxide (DMSO) and bupivacaine with heparin and triamcinolone (B/H/T) instillation groups

	DMSO ($n = 45$)	B/H/T ($n = 146$)	*P* value*
Gravity (mean ± SD)	2.09 ± 1.51	2.44 ± 1.8	0.26
Parity (mean ± SD)	1.71 ± 1.23	1.78 ± 1.37	0.77
Baseline frequency (mean ± SD)	1.8 ± 0.98	2.16 ± 1.16	0.04
Baseline nocturia (mean ± SD)	2.73 ± 1.42	2.13 ± 1.50	0.01
	N (%)	N (%)	
Baseline levator spasm, *n* (%)	9 (20)	49 (33.56)	0.08
Parity >=1, *n* (%)	31 (75.61)	104 (74.29)	0.95
Fibromyalgia, *n* (%)	4 (8.89)	11 (7.64)	0.76
Pelvic pain, *n* (%)	37 (82.22)	110 (75.34)	0.34
Pelvic pressure, *n* (%)	16 (35.56)	54 (36.99)	0.86
Prior pelvic floor physical therapy, *n* (%)	6 (13.64)	20 (13.99)	0.95
Prior pelvic surgery, *n* (%)	19 (42.22)	56 (38.36)	0.64
OAB medications, *n* (%)	16 (35.56)	51 (34.93)	0.94
OAB other treatment, *n* (%)	2 (4.44)	4 (2.74)	0.63
Elmiron medications, *n* (%)	3 (6.67)	9 (6.16)	1

SD standard deviation, *OAB* overactive bladder

* *P* value < 0.05 indicates statistically significant

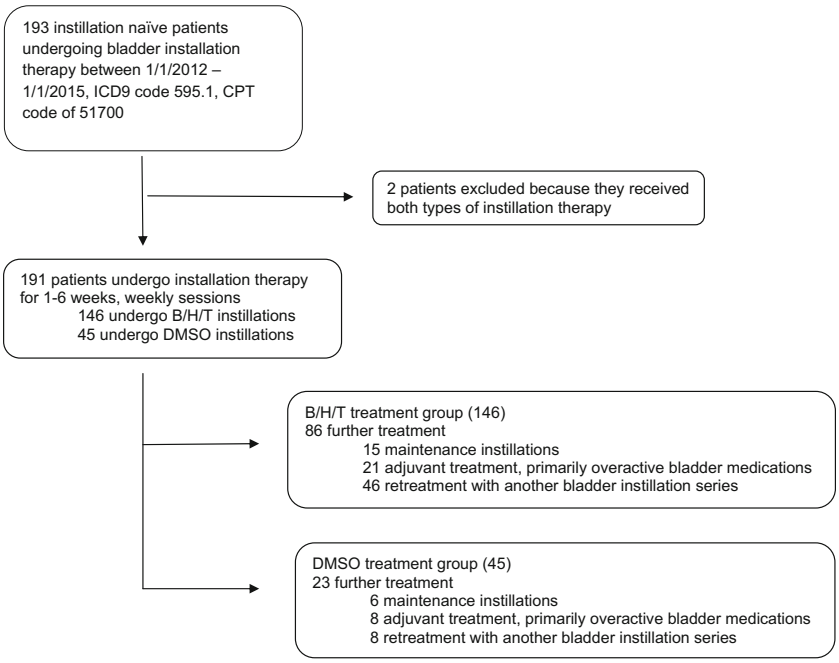

Fig. 1 Description of study participants

voids increased and the number of nighttime voids decreased, they reported greater overall percent improvement (rho = −0.55, $p < 0.00$).

Secondary outcome: daytime voiding frequency and nocturia

The secondary outcomes address changes in daytime voiding and nocturia between groups. At each visit, patients were asked how often they void during the day and wake at night to void. Patients undergoing DMSO treatment had a mean increase of 1.5 h between daytime voids ($p < 0.00$). and those with B/H/T had a mean increase of 1.4 h ($p < 0.00$). There was no significant difference between groups ($p = 0.05$) (Table 2).

For nocturia, only the DMSO group had a statistically significant decrease of 37%, or 0.59 decrease in episodes per night ($p < 0.00$). The B/H/T group had an 8% decrease, or 0.85 decrease in episodes per night that was not significant. This is because the confidence interval (CI) for the B/H/T group included 1.00. Comparing the percent decrease of nighttime voiding episodes between groups, DMSO patients had a significant decrease in episodes from basline ($p = 0.03$) (Table 2).

Who responds to therapy?

Overall, 103 of 191 patients (53.9%) reported >50% response to bladder instillations. Patients with BPS/IC who had >50% (103) response to any bladder instillation treatment were less likely to have previous vaginal surgery. Patients who reported >75% (57) improvement in symptoms were less likely to have levator spasm on exam but more likely to report pelvic pressure. Logistic regression of baseline characteristics for all 191

Table 2 Primary outcome comparison of overall percentage improvement, daytime voiding frequency, and nocturia reported after completion of bladder instillation series between dimethyl sulfoxide (DMSO) and bupivacaine with heparin and triamcinolone (B/H/T) treatment groups

DMSO (n = 45)			B/H/T (n = 146			DMSO vs. B/H/T		
Estimate ± SE	95% CI	*P* value	Estimate ± SE	95% CI	*P* value	Estimate ± SE	95% CI	*P* value
62.66 ± 4.56	(53.71, 71.61)	**<.0001**	50.67 ± 2.52	(45.73, 55.62)	**<.0001**	11.99 ± 5.21	(1.76, 22.21)	**0.0217**
IR ± SE	95% CI	*P* value	IR ± SE	95% CI	*P* value	IRR ± SE	95% CI	*P* value‡
Day Frequency (every x hours) change from baseline								
1.54 ± 0.22	(1.17, 2.04)	**0.0024**	1.38 ± 0.11	(1.19, 1.61)	**<.0001**	1.12 ± 0.18	(0.81, 1.53)	0.4974
Nocturia (episodes/night) change from baseline								
0.59 ± 0.08	(0.45, 0.78)	**0.0002**	0.85 ± 0.07	(0.72, 1.00)	0.053	0.69 ± 0.11	(0.50, 0.95)	**0.0233**

Significant values are shown in bold

SE standard error, *IR* incidence rate, *IRR* incidence rate ratio, *CI* confidence interval

Table 3 Comparison of time to retreatment and type of retreatment between dimethyl sulfoxide (DMSO) and bupivacaine with heparin and triamcinolone (B/H/T) treatment groups

	DMSO *N* (%) (*n* = 45)	B/H/T *N* (%) (*n* = 146)	*P* value
Retreatment	23 (51.11)	85 (58.22)	0.4003
Type of retreatment			
Prevention (maintenance instillations)	6 (26.09)	15 (18.07)	
Adjuvant treatment (overactive bladder medications, pelvic floor physical therapy, trigger point injections, gabapentin or other pain medications)	8 (34.78)	21 (25.3)	
Retreatment with Elmiron, bladder instillations, or cystoscopy with hydrodistention	8 (34.78)	46 (55.42)	
Other	1 (4.35)	1 (1.20)	

patients showed that patients who had previous surgery [odds ratio (OR) = 1.79, CI 0.96–3.35, $p = 0.07$] and levator spam on exam (OR = 1.905, CI 0.99–3.68, $p = 0.06$) were more likely to have <50% improvement. Patients who had levator spam (OR = 1.90, CI 0.91–3.95, $p = 0.09$) were also more likely to have <75% improvement. While these OR were not significant, they represent a clinically significant change from baseline. There was no difference in baseline characteristics or the confounders pelvic pain, pelvic pressure, cystoscopy findings, or fibromyalgia between instillation treatment types.

Time to further treatment

Of the 45 patients who received DMSO instillations, 23 (41%) had further treatment for their symptoms. Six patients (26%) had prevention or maintenance instillations at either a 2- or four-weekly interval. Eight patients (35%) had adjuvant treatment primarily with medication for overactive bladder, and eight (35%) had retreatment with additional series of instillations. Of the 146 patients in the B/H/T group, 86 (59%) had further treatment after their initial series. Fifteen patients (18%) had prevention instillation treatments, 21 (25%) had adjuvant treatment with primarily overactive bladder medications, and 46 (55%) had a retreatment series with bladder instillations. Between groups, there was no significant difference in retreatment patterns ($p = 0.40$) or time to retreatment (0.58). The mean time to retreatment for patients who underwent DMSO was 18 weeks and for B/H/T, 17.4 weeks (Table 3). While we provide follow-up data on patients returning to our center, we do not know whether patients presented to other centers for further or additional care. Patients undergoing DMSO therapy had more severe symptoms than those undergoing B/H/T. Additionally, many providers recommended maintenance instillations to patients with more severe symptoms or those helped by the therapy. It was difficult to compare retreatment between groups.

We completed a subanalysis of patients who did not complete the full 6-week course to investigate whether a minimum number of instillations is needed for symptom improvement. Patients who reported >50% improvement completed 4–6 instillations. As overall treatment response decreased from >50, 1–50, and 0%, the number of patients who completed 4–6 treatments decreased from 100 to 95.38 and 75%. This association was significant ($p < .00$). We were unable to compare groups due to low numbers when stratified.

Discussion

In our study, we found that patient-reported percentage improvement overall and in nocturia was significantly improved with DMSO over B/H/T. Instillation treatment with either one increases time between daytime voids, decreases number of nighttime voids, and results in significant improvement in overall symptoms. When comparing treatment groups, DMSO showed greater improvement in nighttime voiding episodes and greater percentage improvement in overall symptoms.

DMSO is a treatment for BPS/IC that has been approved by the US Food and Drug Administration (FDA) since 1997 but is not well studied. Although the exact mechanism by which DMSO works is unknown, it is thought to decrease inflammation, cause detrusor relaxation, and cause temporary urothelial injury [5]. It is commonly thought to cause increased pain and be poorly tolerated, but this has not been substantiated in the literature. There is a paucity of literature comparing DMSO with other instillation regimens. However, two randomized control trials are reported in the literature comparing DMSO with placebo: Perez-Marrero et al. found that when patients underwent treatment with DMSO every 2 weeks for 4 sessions and were evaluated by a blinded clinician 1 month after treatment, 93% of DMSO patients were improved compared with 35% of placebo patients when successful treatment was defined as a 50% improvement in bladder capacity [6]. Peeker et al. conducted a randomized double-blind control trial comparing DMSO to bacillus Calmette-Geurin (BCG) instillations and found significant reduction in bladder pain in patients receiving DMSO [7]. Gafni-Kane

et al. showed an increase in bladder capacity, intervoid intervals, and nocturia episodes from baseline in patients treated only with DMSO [3].

With regards to B/H/T instillation, several studies show improved bladder capacity with heparin treatment and, more recently, with mixtures of heparin and lidocaine. Parsons et al. conducted a double-blind crossover study using a lidocaine and heparin mixture. They found that 50% of patients had decreased urgency and frequency and 42% reduced pain with a heparin and bupivacaine mixture. This is compared with 13% decrease in urgency and frequency with 21% reduction in pain after placebo. Other studies have compared heparin alone or triamcinolone alone to lidocaine, with positive findings [2, 8, 9].

The major strength of our study is that it is the first to directly compare DMSO with B/H/T bladder instillation treatments. We conducted a thorough literature search using PubMed database without time restrictions and the keywords instillation, interstitial cystitis, painful bladder, and treatment without restricting language or dates. Another strength is that our center keeps standardized records, making a retrospective review of a large number of patient charts accurate and feasible. Overall, a large percentage of our patients completed their treatment paths and returned for follow-up, which limits bias. Limitations are its retrospective design and our inability to capture unrecorded data, such as pain scores. Our primary outcome measure was patient-reported percentage improvement, which was consistent but not standardized across all providers. A pain scale was not consistently used at instillation visits or at the follow-up visit. Additionally, the higher initial severity of daytime frequency and nocturia in patients undergoing DMSO treatments compared with patients undergoing B/H/T reflects a bias in our practice of offering DMSO to patients with more severe urgency, frequency, or pain. However, although this bias could have worked against the DMSO treatment group, it did not. While we were unable to meet the numbers for our power calculation, we were able to show significance in several comparisons.

As there are no universally agreed-upon treatment regimen for bladder instillations in the literature, we studied the medications our center uses, which may limit generalizability. Our study was not designed to determine an optimal treatment regimen, but investigation into this topic would be helpful for guiding clinical practice.

In conclusion, considerations for DMSO treatment in patients with increased nocturia could improve treatment results. Our center is currently conducting a prospective randomized controlled trial comparing the above treatment regimens. Results of that study will answer many questions generated in this paper.

Compliance with ethical standards

Funding No outside funding was received.

Conflicts of interest None.

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