



Bladder Hydrodistention Does Not Result in a Significant Change in Bladder Capacity for Interstitial Cystitis/Bladder Pain Syndrome Patients

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OBJECTIVE	To assess the impact of multiple (2 or more) bladder hydrodistentions (HODs) on anesthetic bladder capacity (BC) in a large cohort of interstitial cystitis/bladder pain syndrome (IC/BPS) patients. Urinary HOD under anesthesia is a third line therapeutic approach used to treat patients with IC/BPS. There is some concern that performing multiple therapeutic HODs may be contraindicated due to the potential for contributing to a diminished BC over time.
MATERIALS AND METHODS	This is a retrospective chart review of IC/BPS patients from a single institution who had undergone 2 or more bladder HOD procedures. Patient demographic and clinical data, including BC under anesthesia, were retrieved from patient charts for analysis. Least squares regression slopes of BC under anesthesia were calculated and used to estimate within-patient BC changes over time.
RESULTS	Data from 168 patients (637 HOD procedures) were included for analysis. The average change in BC, 0.52 ± 8.33 mL/mo, was not significantly different from 0 ($P = .42$). Linear regression analyses did not identify any significant correlation between BC over time with: (1) age, (2) number of HODs, (3) frequency of HODs, (4) average BC, (5) length of time with an IC/BPS diagnosis, or (6) length of time during which the patient's BC was evaluated. Moreover, there was no difference in BC change over time in patients with and without Hunner's lesion ($P = .86$).
CONCLUSION	Multiple therapeutic HODs, over several years, do not result in a significant change in BC in IC/BPS patients. UROLOGY 132: 81–86, 2019. © 2019 Elsevier Inc.

Urinary bladder hydrodistention (HOD) is a procedure used both for diagnostic and therapeutic purposes in interstitial cystitis/bladder pain syndrome (IC/BPS) patients. At present there is no uniform metric for deciding which patient should undergo HOD, nor any standardized HOD procedure,¹⁻³ likely accounting, at least in part, for the discordant views among clinicians regarding the usefulness and therapeutic efficacy of HOD. There is

some concern about the long-term impact of multiple HODs due to the proposed mechanism of therapeutic action for HOD (specifically local neurologic damage^{2,3}), findings that demonstrate bladder stretching can lead to contractions and alterations in bladder contractility,^{4,5} and the paucity of high quality data assessing HOD therapy.⁶ One specific concern is that repetitive bladder "damage" resulting from multiple HODs might lead to bladder fibrosis and result in decreased bladder capacity (BC).

Kirk et al⁷ investigated the impact of HODs on symptom parameters and BC in a retrospective study and within their cohort they found that HOD therapy did not change BC in the 119 patients that had multiple HODs. The goal of the present study was to assess the impact of multiple HODs on BC within a larger cohort of patients ($n = 168$) and within the context of HOD-specific and IC/BPS disease-specific parameters. Such an analysis is crucial to the interpretation of the impact of HODs on BC as there may be differences according to the intensity or longevity of HOD therapy

Funding: Funding for this study was provided, in part, by the Interstitial Cystitis Association (Pilot Research Program Grant Award; SJW) and the NIDDK (R21DK106554-01; SJW).

Conflicts Of Interest: Nothing to disclose.

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Submitted: April 12, 2019, accepted (with revisions): June 24, 2019

and/or a differential impact on patients with more severe IC/BPS pathology. The primary hypothesis was that multiple HODs will not significantly change BC in IC/BPS patients and the secondary hypothesis was that neither the longevity of HOD therapy nor severity of IC/BPS would influence the impact of HOD on BC.

MATERIALS AND METHODS

Subject Recruitment

Participants were recruited as previously described in Walker et al.⁸ Briefly, subjects were recruited to participate in an IC/BPS registry from the Urology Clinic at Wake Forest Baptist Hospital. Experimental subjects prospectively enrolled in this study were males and females between 18 and 80 years of age who were undergoing therapeutic HOD treatment for IC/BPS. Patients were excluded from study if they had a history of bladder, uterine, ovarian or vaginal cancer, urethral diverticulum, spinal cord injury, stroke, Parkinson's disease, multiple sclerosis, spina bifida, radiation cystitis, cyclophosphamide treatment, an active genital herpes outbreak, or if they were currently pregnant. In addition to providing demographic data, all subjects included in the registry allowed access to their detailed medical history. Information regarding patient demographics was collected from the patient charts. The *date of diagnosis* was provided by the patient and refers to the date that they were first diagnosed with IC/BPS by a clinician. *Duration of diagnosis* refers to the number of months between the date of diagnosis and the date of HOD.

Bladder Hydrodistention

Patients were offered HOD if they demonstrated symptoms suggesting the presence of Hunner's lesion or if they failed to respond adequately to first and second line therapies such as diet, stress management, physical therapy and/or medication. Patients who felt they had had a good response to HOD were offered the option of repeat HOD when symptoms returned. Patients receiving botox injections under general anesthesia were offered simultaneous HOD, usually every 6 months.

Bladder HOD was performed according to NIDDK parameters and based on AUA guidelines^{9,10} with the patient under general anesthesia. Anesthesia was delivered via laryngeal mask airway or endotracheal tube without muscle relaxation and with appropriate monitoring with a bispectral index monitor to ensure complete general anesthesia. To ensure no leakage around the cystoscope, digital pressure was placed periurethraly and the bladder was filled with sterile water to a pressure of 100 cm and held for 5 minutes. Following HOD the bladder was drained and the anesthetic BC was recorded. The bladder was then

reinspected for Hunner's lesions. All observed Hunner's lesions were fulgurated at the time of identification. All surgical procedures were performed by a single clinician (RJE).

Statistical Analysis

Simple linear regressions were performed to assess the impact of patient and HOD parameters on the least squares estimated slope of BC change over time. Any parameters that were found to have an impact with P value $\leq .1$ were chosen for inclusion in a multi-linear regression model. An independent t test was used to assess if there was a difference in the slope of BC change in patients who had any Hunner's lesion-positive HODs during the study. Independent t tests were also performed to assess if there was a statistically significant difference in BC change according to whether the patient ever had a Hunner's lesion, a BC recorded under 400 cc, or had a botox treatment during the study. Statistical significance for all final analyses was indicated by $P \leq .05$.

RESULTS

Descriptive Findings

Data from 168 patients (637 HODs) were included in the study. Patient demographics are shown in Table 1. The number of HODs per patient ranged from 2 to 20 with an average of 3.8 ± 2.4 . A total of 17 patients (10.12%) were found to have a Hunner's lesion-positive HOD at some point in the study. The average time between HODs was 16.7 ± 11.3 months (range = 2.9-60.1 months). The average span of time that a patient's BC was monitored (the time between their first and last HOD in the study) was 36.5 ± 21.2 months.

Impact of Hydrodistention Therapy on Bladder Capacity Change

Overall, there was no significant change in BC associated with repeat HOD therapy. The slope of BC change over time (including all patients and all HODs) was 0.52 ± 8.33 mL/mo, which was not statistically different from 0 ($P = .4219$). The distribution of BC change slopes is depicted in Figure 1. The outliers of the BC change distribution represent patients with fewer recorded HODs within the study. Even as the number of HODs for a patient increases, the BC change effectively remains zero (Supplementary Table 1). Neither the average time between HODs (a measure of frequency; $P = .705$) nor the total number of HODs ($P = .376$) (Fig. 2A) was associated with a significant change in BC over time (Supplementary Table 1). Further, the length of time that a patient's BC was tracked (eg, months vs years) did not impact the ability to capture significant changes in BC over time (Fig. 2B; $P = .315$).

Table 1. Patient demographics and HOD statistics

Statistic	Number (%)	Mean \pm SD	Median	Range
Age	—	46.75 \pm 12.97	46	20-83
Female	162 (95.29)	—	—	—
Duration of IC/BPS Dx (mo)	—	134.78 \pm 79.42	114	29-378
Total no. of HOD	—	3.79 \pm 2.43	3	2-20
Time between first and last HOD in study (mo)	—	36.51 \pm 21.22	35.8	2.87-107.53
Average time between HOD (mo)	—	16.66 \pm 11.31	13.36	2.87-60.1
Average BC for a patient (mL)	—	842.84 \pm 310.43	813.33	300-1750
Had any BC <400 cc	14 (8.33)	—	—	—
Had any Hunner's lesions	17 (10.12)	—	—	—
Had any botox treatments	61 (36.31)	—	—	—

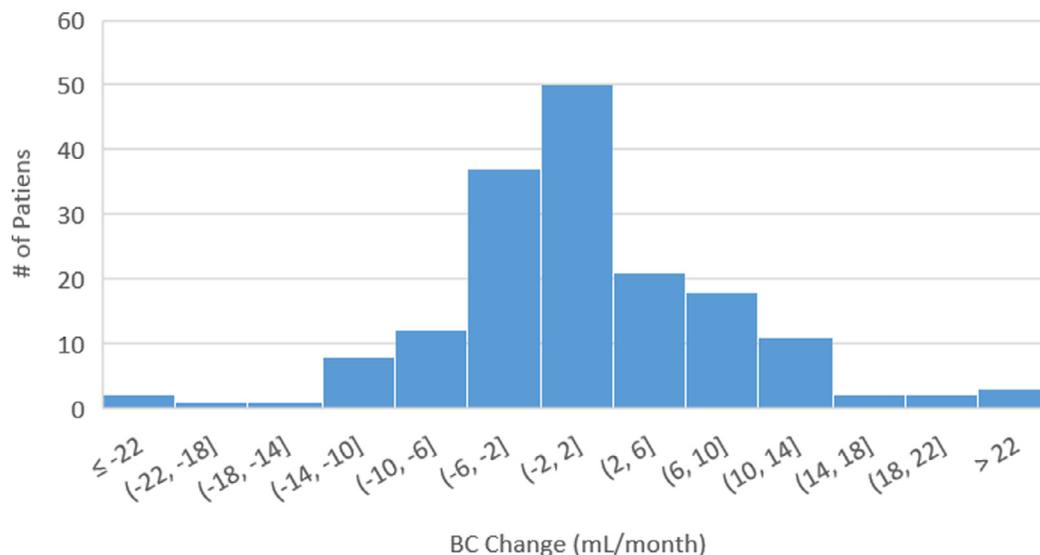


Figure 1. BC change (mL/mo) for all patients. Numbers on the x-axis represent a range (eg, [-2, 2] indicates a range in the change in BC, from a decrease of less than 2 mL/mo to an increase of 2 mL/mo following an HOD). (Color version available online.)

Bladder Capacity Change by Indicators of Disease Longevity or Severity

Three indicators of the extent of IC/BPS disease (duration of IC/BPS diagnosis, anesthetic BC, and the presence of Hunner's lesions) were analyzed for their impact on BC. Neither the length of time since diagnosis of IC/BPS ($P = .607$) nor average BC ($P = .283$) was significantly correlated with BC (Supplementary Table 1). Additionally, the analysis of BC slopes in patients who had an HOD with Hunner's lesion at some point during the study compared to those who never had a Hunner's lesion during the study did not show any significant difference between the groups (0.90 v. 0.47 mL/mo, $P = .860$; Fig. 2C).

Subgroup Analyses

Table 2 demonstrates the demographics of 2 patient subgroups who are generally considered to have advanced IC/BPS bladder pathology; patients who had at least 1 Hunner's lesion and those who had at least 1 significantly low BC <400 cc. Neither group had a statistically significant change in BC. Table 2 also displays the demographics of patients who received botox treatments during the study. In total there were 61 patients who received botox treatments at the time of their HODs in the study. Overall, there was no statistically significant change in BC within patients who received botox (P value = .514).

DISCUSSION

This retrospective analysis of 168 patients (637 HODs) indicates that repeated HODs do not result in an iatrogenic decrease in BC for the general IC/BPS population. Confirming the relative safety of repeat procedures is important for the viability of HOD as a therapeutic strategy for IC/BPS.¹ Neither indicators of the duration or severity of disease, nor the frequency or total number of HOD treatments, had a statistically significant impact on

BC. The findings in this report are consistent with those from the recent study by Kirk et al wherein the analysis of 119 patients with multiple HOD also found no significant change in BC.⁷ The only procedural difference between the 2 studies is that the protocol used in this study elicited HOD to capacity once for 5 minutes whereas in Kirk et al⁷ HOD was performed twice in 1 session for 2 minutes each time. This difference in protocol did not affect the overall comparative findings.

An important difference between this study and Kirk et al⁷ is the inclusion here of an analysis of differential impacts of multiple HOD therapy. This is the first study to evaluate the impact of HOD on BC according to HOD-specific and disease state-specific parameters. There was no subgroup of IC/BPS patients that was found to be vulnerable to a decrease in BC from HOD therapy. In the subgroup that received botox injections, the results showed that there was no significant impact of botox injection on BC. However, we note that the findings for the specific subgroup analysis of patients with Hunner's lesions or those with BC <400 cc are not sufficiently powered (with <20 patients per group) to draw definitive conclusions.

In addition to the general safety of HOD therapy, our analysis demonstrated that there was no iatrogenic decrease in BC experienced by patients regardless of how frequently or how many times they received HOD. This is significant because at this time there are no standard recommendations as to the frequency or total number of HOD procedures that a patient can/should receive. While these data provide support for the safety of repeat HODs, there is certainly a need to assess what frequency and total number of HODs is therapeutically effective for patients. Although several studies have reported symptom

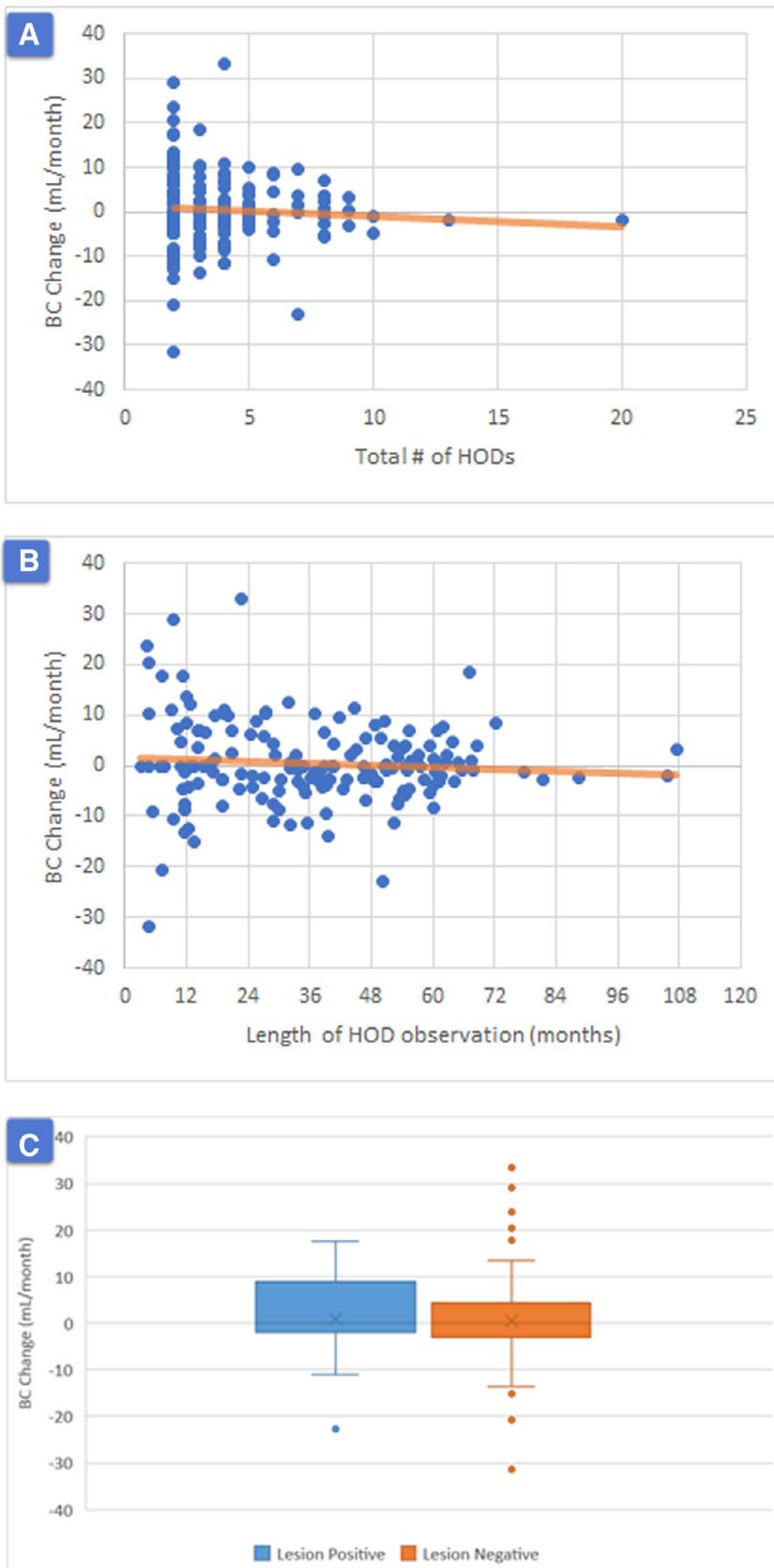


Figure 2. (A). Change in the bladder capacity over time as it relates to the total number of HODs recorded for the patient in the study ($P= .376$); orange line represents the least squares regression slope. (B). The change in bladder capacity over time as it relates to the time between the patient's first and last HOD in this study ($P= .315$). (C). The change in bladder capacity over time for patients who had at least 1 HOD that was positive for a Hunner's lesion vs those who were never Hunner's lesion positive at any time during this study ($P= .860$). (Color version available online.)

Table 2. Demographics and HOD statistics for 3 patient subgroups: (1) had at least 1 Hunner's lesion observed in the study; (2) had at least 1 BC <400 cc; (3) received at least 1 Botox treatment. P value > .05 indicates the average change in BC is not different from 0

Statistic	At least 1 Hunner's Lesion		At least 1 BC <400 cc		At least 1 Botox treatment	
	Number (%)	Mean ± SD	Number (%)	Mean ± SD	Number (%)	Mean ± SD
Age	—	62.12 ± 12.84	—	55.79 ± 11.11	—	45.41 ± 11.78
Female	16 (94.12)	—	13 (92.86)	—	57 (93.44)	—
Duration of IC/BPS Dx (mo)	—	99.92 ± 50.49	—	106.36 ± 67.30	—	145.51 ± 78.14
Total no. of HOD	—	4.29 ± 2.89	—	3.93 ± 2.30	—	4.66 ± 2.82
Time between first and last HOD in study (mo)	—	27.70 ± 17.36	—	24.50 ± 14.48	—	40.41 ± 21.82
Average time between HOD (mo)	—	10.83 ± 7.31	—	9.82 ± 6.85	—	13.51 ± 9.39
Average BC for a patient (mL)	—	543.50 ± 236.55	—	414.49 ± 91.24	—	847.9 ± 325.48
Had any BC <400 cc	6 (35.29)	—	6 (42.86)	—	5 (8.2)	—
Had any Hunner's lesions	—	—	—	—	4 (6.56)	—
No. of Hunner's lesion positive HODs per patient	—	2.47 ± 1.46	—	—	—	0.16 ± 0.82
Had any botox treatments	4 (23.53)	—	6 (42.86)	—	61 (100)	—
Average no. of botox doses	—	0.56 ± 1.21	—	1.43 ± 2.65	—	2.84 ± 2.18
Cumulative botox dose	—	81.25 ± 207.2639	5 (35.71)	250 ± 540.3	—	413.61 ± 415.68
Average change in BC	—	0.90; P value = .703	—	1.22; P value = .615	—	0.66 ± 7.82; P value = .514

improvement in IC/BPS patients that had initial and repeat HOD,^{7,11,12} questions regarding the overall benefit of therapeutic HOD for IC/BPS continue to persist, largely due to the lack of compelling evidence-based data regarding efficacy.⁶

There are several limitations to this study that relate to methodology and scope. First, this is a retrospective study that utilized data from patients who received HODs at various frequencies and across a wide range of total HOD procedures. This limits our power and therefore the ability to make strong predictions about outlier patients such as the 8 males in the study and the 1 patient with more than 15 HODs. The study did not account for the amount of non-HOD therapy that patients received for IC/BPS which would be an important parameter of disease severity and would help identify the impact of HOD on BC in refractory cases. Additionally, we were not able to account for any HOD therapy a patient may have received prior to presenting to our clinic for IC/BPS management. As noted previously, our study focused on the impact of HOD on BC but it was not designed to assess repeat HOD efficacy, an important parameter in assessing the appropriateness of a therapy. Lastly, the finding that multiple HODs are "safe" (ie, do not result in a significant change in anesthetic BC) may be most appropriate when applied to the general IC/BPS population because even though we found no change in BC for "severe" patients (ie, those with Hunner's lesions and/or a low anesthetic BC) the numbers in these subgroups were modest.

The strengths of this study include the relatively large sample size and a consistent HOD protocol. Figure 2A is illustrative of the potential for a mischaracterization of the impact of HOD on BC. This figure shows that BC change over time can vary widely when there are fewer HOD data points available. Specifically, patients with fewer HODs can demonstrate significant changes in BC that are not reflected in the larger data set. The ability of this study to analyze a relatively large cohort of patients who underwent multiple HODs gives both the advantage of larger numbers and an analysis of patients with numerous HODs. This perspective reveals the overall lack of impact of HOD on BC that may be much more difficult for an individual practitioner to observe in a small group of patients receiving few HODs.

In addition to measuring the change in BC over time, we also assessed the relationship between the total number of HODs, as well as the frequency of HODs, on BC. This unique analysis provides insight into the impact that differing HOD regimens may have on BC. This study is also the only study to date to assess the impact of repeat HOD on BC according to measures of IC/BPS severity and duration. Assurance that repeat HOD does not adversely impact patients with long standing IC/BPS and/or with scarred, diminished-capacity bladders (from severe bladder-centric IC/BPS) is crucial to ensuring a practitioner's ability to provide safe therapies for all IC/BPS patients, especially for the subpopulation of patients with an already diminished BC.

CONCLUSION

HOD is a safe therapeutic procedure that does not negatively impact BC in the general IC/BPS population. This study demonstrates that this safety extends to patients with mild to severe IC/BPS, for the newly-diagnosed, and may extend to those with longstanding IC/BPS. While we did not identify specific safety parameters regarding HOD frequency or total number of procedures for IC/BPS patients, one may exist, especially for patients with severe bladder pathology. The results of this study, when combined with patient reports of HOD efficacy, support the continued use of multiple-HOD as a third line therapy for some IC/BPS patients.

Acknowledgments. The authors thank the study participants.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urology.2019.06.031>.

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