Transvaginal Photobiomodulation Improves Pain in Women with Pelvic Muscle Tenderness and Interstitial Cystitis/Bladder Pain Syndrome: A Preliminary Observational Study

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PURPOSE Interstitial Cystitis/ Bladder Pain Syndrome (IC/BPS) is characterized by pelvic/bladder pain, associated with pelvic muscle tenderness, urgency, frequency, and dysuria. Prior studies show that transvaginal photobiomodulation (TV-PBM) reduces pain in women with chronic pelvic pain (CPP). Our objective was to obtain preliminary data on treatment effect and adherence, in women with IC/BPS who selected TV-PBM therapy for management of pelvic pain.

MATERIALS AND METHODS Before-and-after observational cohort study of women with IC/BPS who received TV-PBM in 17 US practices. Pain was measured using a 0-10 numeric rating scale (NRS). The primary outcome was a minimal clinical important difference (MCID); reduction of overall pelvic pain severity by ≥2 NRS points from baseline compared to after 8 treatments. Cohen d coefficient measured effect size (low effect size d<0.2, medium 0.2<d<0.8, and high d>0.8).

RESULTS Of 140 patients with IC/BPS who self-selected to start TV-PBM therapy, 89.3% (n=125) completed 4 treatments and 59.3% (n=83) completed 8. Improvement ≥1 NRS point was reported by 73.5% (n=61) and meaningful improvement (≥2 points) was reported by 63.9% (n=53) after 8 treatments. In this group, patients with severe / moderate pain decreased from 83.1% (n=44) to 38.5% (n=20); p<0.001. Pain levels decreased as follows: overall pelvic pain MCID=-2.7, d=1.07, pain with urination MCID=-2.6, d=1.0; pain with exercise MCID=-2.6, d=0.91, pain with intercourse MCID=-2.5, d=0.82.

CONCLUSION In real-world clinical settings, 2/3 women with IC/BPS who opted to undergo TV-PBM therapy reported significant decrease in pelvic pain and dysuria. These findings are promising; however, controlled studies are needed. UROLOGY 170: 14–20, 2022. Published by Elsevier Inc.

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a heterogeneous disorder that affects 2.7% to 6.7% of women and typically presents with pelvic and/ or bladder pain, associated with urinary dysfunction, without identifiable cause.[1,2] Patients with bladder centric IC/BPS may have urothelial disruption (GAG layer defects resulting in increased permeability), neuro immune up regulation (C-fiber and cytokine up regulation), and at least 78% present with pelvic myalgia and high pelvic muscle tone and dysfunction.[3,4] It is thought that the presence of pelvic dysfunction and myalgia results in symptoms such as voiding frequency, hesitancy, retention, as well as dyspareunia and pelvic pressure.[1,3]

Given that pelvic muscle dysfunction is frequently found in patients with IC/BPS, the American Urologic

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Common Language Summary: *Vaginal photobiomodulation (PBM) is a type of non-ablative laser therapy that has been shown to reduce chronic pelvic pain symptoms. This preliminary study evaluated the effectiveness of PBM in women with IC/BPS and pelvic muscle tenderness. We found that PBM significantly reduced pelvic pain and bladder symptoms for 2/3 of women who selected and completed the therapy.*

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Association (AUA) guidelines recommend pelvic physical therapy (PT) for patients with IC/BPS.[1] Despite the potential benefits of PT, access to this type of therapy in real-world clinical settings is limited. Additionally, effect is dependent upon the experience of the therapist, the techniques used, and adherence to therapy which is often limited. Unfortunately, other treatments currently available for IC/BPS (pharmacotherapy, neuromuscular blockade, and neuromodulation) also have minimal effect on bladder symptoms (urgency, frequency, nocturia) and no effect on pain.[5] Therefore, innovative therapies are desperately needed.

Photobiomodulation (PBM), previously referred to as Low-Level Laser Therapy (LLLT), uses near-infrared (NIR) light to target a mitochondrial chromophore, cytochrome c oxidase (COX). NIR activation of COX initiates a chain of intracellular chemical reactions resulting in analgesia, improved oxygenation, reduced inflammation and edema and muscle relaxation.[6] Many randomized controlled trials (RCTs) and systematic reviews have shown that PBM improves pain in musculoskeletal conditions such as low back pain, fibromyalgia, knee, and shoulder pain.[6-8] Based on the documented benefits of PBM for treating non-pelvic musculoskeletal pain, a transvaginal photobiomodulation (TV-PBM) laser system called SoLá Pelvic Therapy (SPT) (Uroshape, LLC) was developed and introduced into clinical practice in 2019 for the treatment of pelvic pain associated with pelvic muscle tension. This device is an FDA-cleared class IV near-infrared laser, capable of transmitting at both 810nm and 980nm wavelengths. The NIR laser creates non-ionizing and non-thermal effects that avoid serious side effects, such as vaginal scarring or burns, reported when ablative lasers (CO_2 and Erbium: Yttrium aluminum garnet (Er: YAG) lasers) are used for vaginal conditions such as atrophy, laxity, and incontinence.[9–11] In 2020, Zipper and Pryor demonstrated in an ovine model that SPT can effectively deliver NIR energy to pelvic muscle and bladder tissues.[12] A 2021 pilot study of 13 women with chronic pelvic pain (CPP) demonstrated that 60% experienced clinically significant improvement in pain; this effect was sustained at 3 and 6 months after therapy.[13] A subsequent analysis of 128 women undergoing SPT in clinical settings for CPP diagnoses, showed that 64% of women who had failed previous therapies reported a significant reduction in overall pelvic pain.[14]

Based on these initial studies, we suspected that TV-PBM might also be effective in women with IC/BPS presenting with urgency, frequency, and pelvic pain and / or pelvic muscle tenderness. However, there is no published data to support this hypothesis even though TV-PBM is already integrated into clinical practice. Therefore, the objective of this observational study was to obtain preliminary data on treatment effect measured as change in overall pelvic pain level from baseline compared to pain level after 8 treatments, and treatment adherence, in women with an IC/BPS who *self-selected* TV-PBM therapy for the management of their pain.

MATERIALS AND METHODS

This study was a before-and-after secondary analysis of de-personalized data prospectively collected from women treated with TV-PBM using SPT in 17 geographically diverse US. gynecology practices. Prior to starting treatment, all patients provided informed consent. The study was reviewed by the Western Copernicus Group Institutional Review Board (WCG-IRB study 1326108), deemed minimal risk, and considered exempt from further oversight requirements. In conducting the study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The mechanics of the SPT device have been previously published.[12–14] Briefly, the device is composed of a 15W diode laser that emits 810 and 980nm wavelengths in a spherical array through a single-use sterile vaginal probe. A user interface display allows patients and clinicians to input demographic information, diagnoses, symptoms, and symptom severity using a numeric rating 0-10 scale (NRS). Data is collected at baseline and prior to each treatment (for example, at treatment 4 the patient is recording pain levels following the first 3 treatments).

In clinical practice, the device is used in patients with CPP regardless of the inciting cause of such pain (e.g., IC/BPS, endometriosis, IBS, vulvodynia, dyspareunia). The indication for treatment is CPP and the presence of pelvic muscle tenderness (e.g., levator ani, coccygeus, obturator) is confirmed by single-digit palpation. All study patients were evaluated by a gynecologist with a physical examination to confirm their diagnosis, and to rule out infection and neoplasia. The manufacturer recommends twice-weekly treatments administered over 3-5 weeks in order to deliver optimal results to the maximum number of patients, so long as the patient is not on photosensitizing drugs or pregnant. Patients were allowed to continue concurrent pain therapies, excluding therapies that involved vaginal contact such as vaginal creams, or vaginal PT.

Pain was measured using the 0-10 NRS accompanied by descriptors ranging from 'no pain' at 0 to 'worst pain' at 10 and categorized as 'no pain' if NRS was 0-1, 'mild pain' if NRS was 2-4, 'moderate pain' if NRS was 5-7, and 'severe pain' if NRS was 8-10.[15] The primary study outcome was change in overall pelvic pain level from baseline compared to after 8 treatments (data collected at clinic visit #9). Secondary outcomes included change in pain with urination, exercise, sitting, standing, bowel movements, intercourse, and vulvar pain. Minimal Clinically Important Difference (MCID) was defined as pain reduction ≥2 NRS points. Notably, a 30% decrease in the NRS score has been shown in prior research to consistently represent what patients with musculoskeletal chronic pain describe as 'much better' improvement.[16,17] Because the degree of improvement is also dependent on the baseline level of pain, i.e., patients with lower baseline pain levels may experience a 30% decrease yet this may not seem as significant, we also measured effect size (Cohen d coefficient) to describe degree of improvement. Cohen d is interpreted as low effect size if $d<0.2$, medium if $0.2<d<0.8$, and high if $d>0.8$.

At present, TV-PBM is not reimbursed by insurance. In clinical practice, the manufacturer provides the first two of nine standard treatments for free. This creates an accessible test-treatment pathway in which patients self-select to continue to standard therapy. Our analysis was limited to those patients who were self-selected for standard treatment.

All study participants were required to report overall pelvic pain severity and additional symptoms including, pain with sitting, standing, and exercise, pain with bowel movements,

urination, intercourse, vulvar pain, frequency/ urgency, and urinary incontinence. Since our primary outcome was pain, we excluded patients who reported a baseline NRS pain level ≤ 2.

Statistical significance was determined using Chi^2 and Fisher's Exact test for categorical variables. The paired t-test was used to analyze continuous, normally distributed variables and one sample Wilcoxon ranked sum t-test was used for non-parametric continuous variables such as pain levels (0-10). Statistical significance was set at a two-tailed alpha level of 0.05 and power of 80%.

For multivariable analyses, improvement was defined as a decrease of 2 or more NRS points in overall pelvic pain. Exposure variables included in multivariable models were selected a priori based on whether they may affect chances of improvement. These variables were age, duration of pelvic pain, presence of frequency/urgency and dysuria, duration of dysuria, and presence of 1 or more pain co-morbidities (endometriosis, pain with bowel movements, vulvodynia, vaginismus, and pelvic muscle dysfunction). Because chronic pain therapies are rarely curative, we also calculated the odds of having persistent moderate or severe pain following treatment. All analyses were conducted using Epi Info™ version 7.2 and STATA 16 (StataCorp, LLC); graphs were created using Microsoft Excel.

RESULTS

The patients included in our analysis were treated between June 2019 and December 2021. The original dataset contained data on 3799 treatments administered to 518 patients. Within this cohort, 33.8% (n=175) were diagnosed with IC/BPS (self-reported). Six participants (3.4%) reported a pelvic pain level ≤2 and 29 (16.6%) did not self-select for therapy. Therefore, 140 (82.3%) were eligible for our study and included in the final analysis. Although this was not an experimental study that would allow us to conduct an intention-to-treat analysis, a comparison between the included and excluded groups revealed no baseline differences in age (P=984), overall pelvic pain level (P = .060), pain duration (P=.791), prior treatment with pelvic PT (P=.693), and gynecologic pain co-morbidities such as endometriosis (P = .103), dyspareunia (0.783), and vulvodynia (P=.078).

Among the 140 who self-selected for therapy, 89.3% (n=125) finished 4 treatments and 59.3% (n=83) finished 8 treatments and provided data at the 9th visit. The characteristics of the study cohort, including average pain levels, additional symptoms, and pain co-morbidities are shown in Table 1. Of those who completed 8 treatments, 87.2% (n=75) had one or more additional pain diagnoses including endometriosis, vulvodynia, vaginismus, painful bowel movements, and pelvic myalgia. Regarding urinary symptoms, 83.1% (n=69) also reported having frequency and / or urgency, 73.5% (n=61) had pain with urination in addition to pelvic pain, and 57.8% (n=48) had both frequency / urgency and dysuria.

In the group that completed treatment, 73.5% (n=61) improved by at least 1 NRS point. Clinically significant improvement, ≥ 2 NRS points reduction, was reported by 63.9% (n=53). Changes in pain levels over time and comparisons before baseline and after 8 treatments are depicted in Fig 1. Statistically significant improvements in pain were reported for all pain outcomes. After photobiomodulation, clinically significant improvements were found in overall pain, pain with intercourse, urination, and exercise (Fig 2).

Table 1. Demographic, pain, and pain co-morbidities of the patients included in the analysis (n=83)

Characteristic	Value
Mean Age Years (SD, Median, Range)	48.2 (15.1, 48, 16-75)
Overall pelvic pain severity on 0-10 NRS, mean (SD)	6.7 (2.2)
Pelvic pain duration, n (%)	
<1 year	7 (11.5)
>1 year	5 (8.2)
>2 years	5 (8.2)
>3 years	8 (13.1)
>4 years	36 (59.0)
Urgency / Frequency, n (%)	69 (83.1)
Incontinence, n (%)	29 (34.9)
Pain with urination	61 (73.5)
Pain with urination severity on 0-10 NRS, mean (SD)	5.9 (2.7)
Pain with urination duration, n (%)	
<1 year	8 (9.6)
>1 year	5 (6.0)
>2 years	8 (9.6)
>3 years	10 (12.1)
>4 years	52 (62.7)
Co-morbid pain conditions	
Endometriosis n (%)	16 (19.3)
Dyspareunia n (%)	43 (51.8)
Vulvodynia n (%)	33 (39.8)
Pelvic floor myalgia n (%)	61 (73.5)
Pain with bowel movements	42 (50.6)
Vaginismus	16 (19.3)

In multivariable analysis, the following variables were not associated with clinically significant improvement in overall pelvic pain: longer pelvic pain duration (OR=1.3, 95%CI 0.9-1.7), one or more co-morbidities (OR=1.5, 95%CI 0.5-4.5), presence of dysuria (OR=2.1, 95%CI 0.8-5.4) and longer dysuria duration (OR=1.6; 95% CI 1.1-2.3). Of those who initially reported having urinary frequency/urgency (n=68), 69.9% reported on this symptom again at the end of treatment. In this group, 53.4% (n=36) had improved urgency, 36.2% (n=21) reported no improvement, and 10.3% (n=6) reported worsening urgency.

The percentage of patients with moderate/severe pelvic and urinary pain also decreased significantly after treatment (Fig.3). After treatment, there was a 12% chance of having continued moderate or severe pain, i.e., treatment with TV-PBM reduced the odds of having moderate or severe pain by 88% compared to baseline (OR=0.12, 95%CI 0.06-0.25).

DISCUSSION

This is a preliminary report based on real-world use of TV-PBM for the treatment of pelvic pain in patients with IC/BPS. The prevalence of IC/BPS in patients presenting with CPP at the various clinical sites included in our data set was 34%. Nearly 90% of this cohort had at least one other pain co-morbidity such as endometriosis, vulvodynia, vaginismus, and bowel related pain. The most common symptoms described by IC/BPS patients in our study were frequency and / or urgency and dysuria. These findings suggest that the patients who were part of this analysis are representative of the spectrum of IC/BPS patients seen in clinical practice; a heterogenous population that is

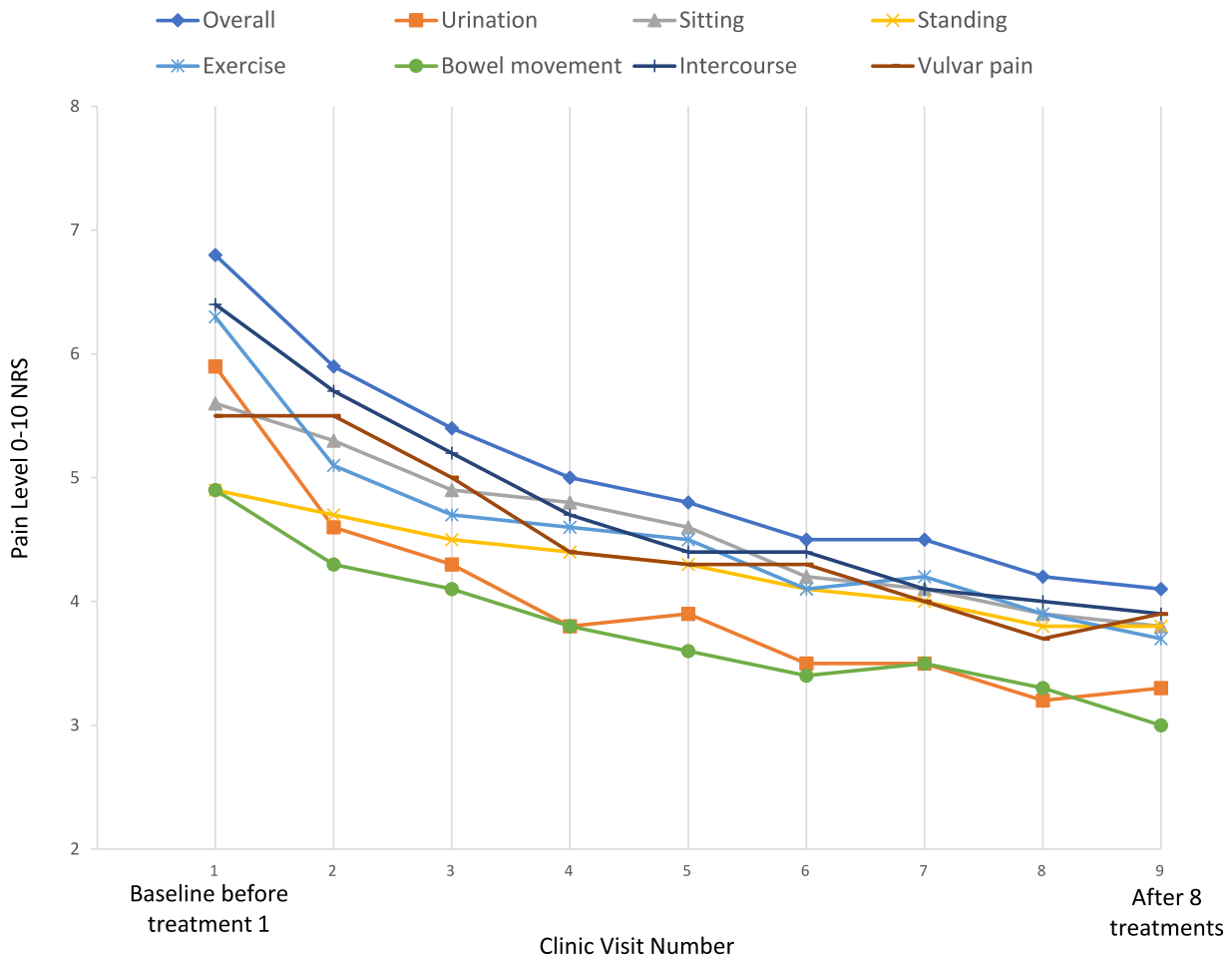

Figure 1. Average pain level at each visit over the of treatment and comparison between baseline pain severity and pain severity after 8 treatments. (Color version available online.)

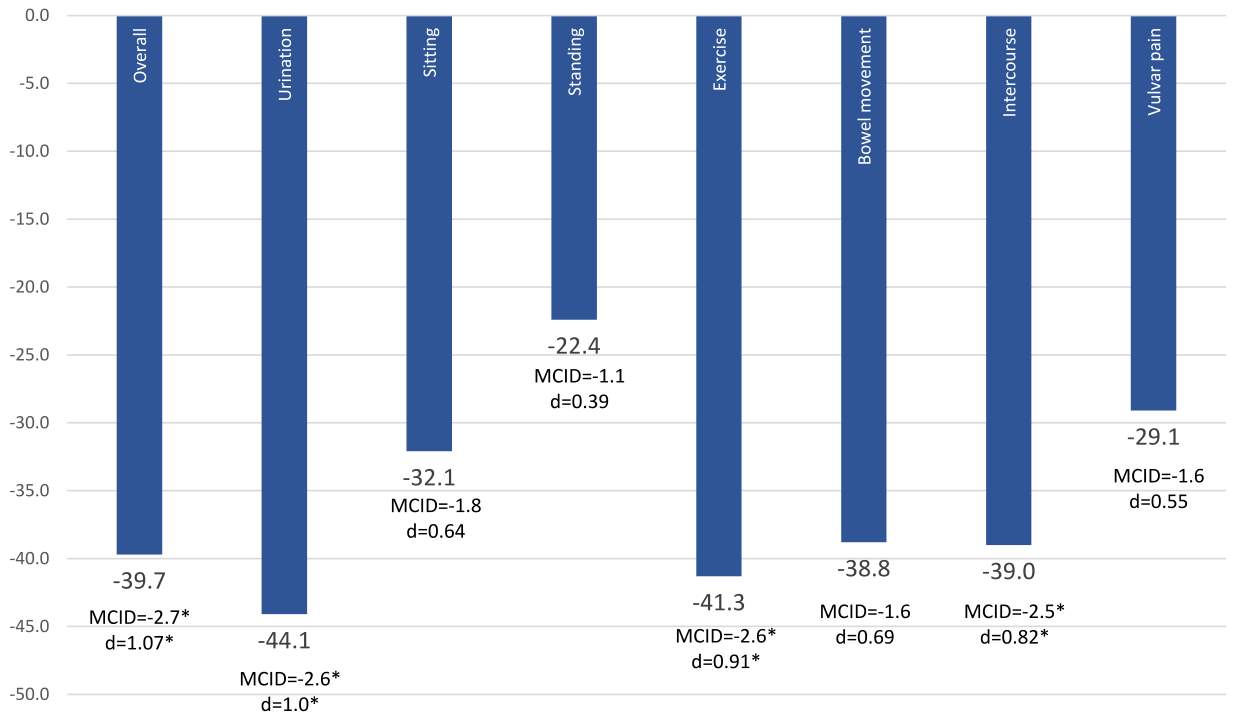

Figure 2. Percentage pain severity decrease, minimally clinical important difference, and effect size, comparing baseline to after 8 treatments. (Color version available online.)

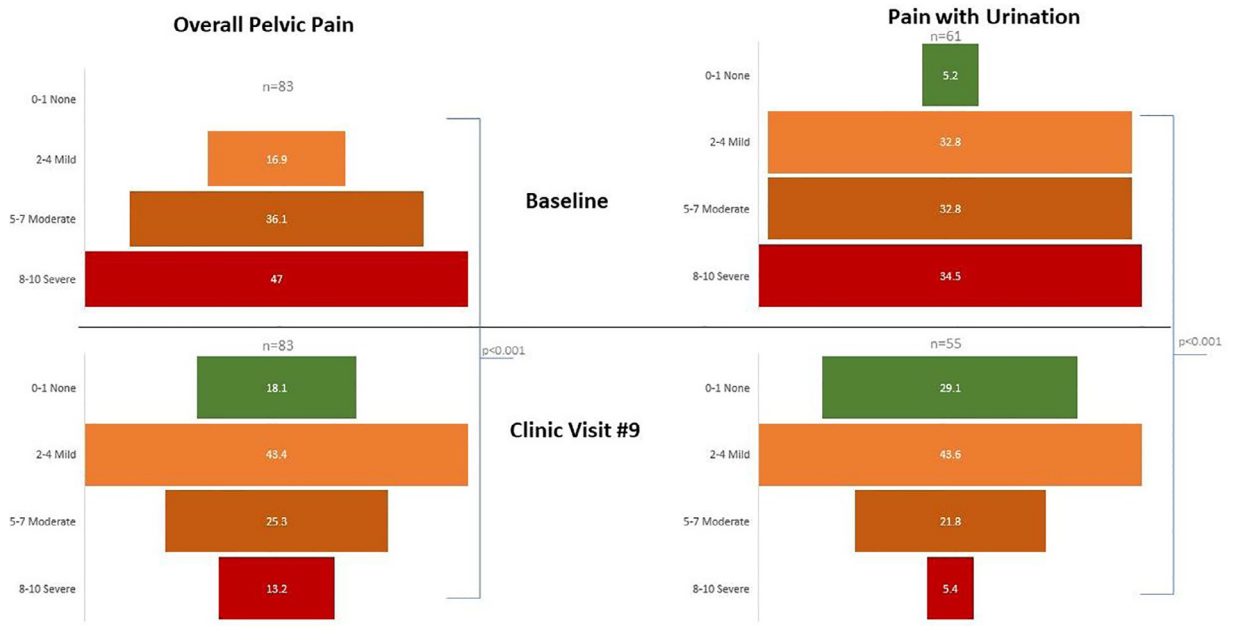

Figure 3. Changes in moderate / severe overall pelvic pain and urinary pain before and after 8 treatments. (Color version available online.)

considered difficult to treat.[1,2,18–21] Despite this, we found that adherence with therapy was relatively high. Approximately 90% completed 4 treatments and 60% completed all recommended treatments. We speculate that discontinuation was likely not related to serious adverse events (none were reported) or cost since participants paid for all treatments prior to initiating therapy. However, participants may have chosen to stop therapy due to time, travel, or access issues, as well as lack of therapeutic effect. Notably, the largest decrease in pain, i.e., time to maximal effect, was noted within the first 4 treatments. Pain levels continued to improve after but improvements were smaller and this may explain the lower continuation rate as treatment progressed.

Although all types of pain demonstrated statistically significant reduction in pain, the largest decrease and effect size was noted in overall pelvic pain, dysuria, dyspareunia, and pain with exercise. After 8 treatments, the number of patients reporting moderate or severe pelvic pain decreased from 83% to 38% and dysuria decreased from 67% to 27%. On average, patients reported 39-44% reduction in pain severity. It is important to note that this represents a decrease from severe/moderate pain to mild or no pain; clinically this is considered a highly significant change. Patients who completed treatment had nearly 90% odds of pain improvement compared to their baseline.

The positive effect seen in this study is consistent with the mechanism of action of photobiomodulation and the potential impact on multiple bladder and pelvic muscle pain generators.[22] In vitro studies show that PBM results in analgesia through reduction in A-delta and C fiber activity, modification of pro-inflammatory cytokines, growth factors and chemokines. Notably, C-fiber activation is thought to be a major contributor to the development of the allodynia that is responsible for the symptom of urinary frequency and bladder pain in patients with IC/BPS.[23] Several studies have demonstrated that photobiomodulation acts on the mitochondria to increase ATP production, release nitric oxide, and modulate reactive oxygen species resulting in improvement in the oxidative stress environment of muscles at the sub-cellular level.[22] The nitric oxide has a direct effect of vasodilation which improves the blood supply to the muscles thus correcting the hypoxia that is thought to be a key trigger to the maintenance of myofascial pain.[22]

Our ability to treat pain in patients with IC/BPS has been limited to few options. A 2020 systematic review analyzing treatment interventions for IC/BPS including pharmacotherapy (e.g., antidepressants, antibiotics, pentosan polysulfate sodium), local anesthetics, behavioral therapies, neuromuscular blockade with Botulinum toxin, denervation, and fulguration, showed that these interventions do impact pain or urinary frequency.[5] Generally the evidence was of very low quality, composed of small samples, yielding small odds of improvement with wide confidence intervals.[5] Although the AUA recommends pelvic PT for IC/BPS, effectiveness remains uncertain. An initial feasibility study demonstrated superiority to a full body western massage, however, the subsequent Randomized Multicenter Clinical Trial (RCT) enrolled 81 women and failed to confirm this effect.[24] Although 59% of participants who underwent pelvic PT reported improvement versus 26% in the global massage group (p=0.000123), there was no significant difference in pain severity, urgency, and frequency between the two groups at the end of the trial.[24] Compliance with PT in a real-world setting is more concerning. Woodburn et al reporting on over 600 referrals by gynecologist to PT, found

compliance to be approximately 20%,[25] much lower than 60% adherence reported by our study.

These preliminary findings suggest that TV-PBM has the potential to significantly reduce pelvic pain, dysuria, dyspareunia, urgency / frequency, and pain with activity in patients with IC/PBS. TV-PBM treatment was able to achieve pain relief in a higher percentage of patients when compared to published results of pelvic PT or placebo and has the advantage of being minimally invasive, easily implementable into clinical practice, and without reported major side effects. Furthermore, adherence with therapy was relatively high, and clinically meaningful improvement in pain was seen in as little as 4 treatments.

The strengths of this study are robust sample size, patient-reported outcomes, contemporaneous data collection that is obtained from real-world clinical settings, and the inclusion of patients who were refractory to prior treatments, i.e., the findings are generalizable to real clinical practice. However, our conclusions are limited by the uncontrolled study design which prevents us from establishing a direct causal link between the use of TV-PBM and improvement in pain. Since patients self-select standard treatment, we may not be accounting for the effect of selection bias and other factors, such as the effect of adjunct therapies and repeated interaction with a healthcare provider, that may play a role in symptom improvement independent of the use of TV-PBM. We also do not know why 17% patients did not self-select standard treatment even though they had similar characteristics to those who did. Reasons for discontinuation may include cost, discomfort, little perceived benefit, and time constraints.

A prior pilot study published by our group shows that the PBM effect may last as long as 6 months,[13] however, in this study we do not have data on long-term outcomes. Additionally, the presence of pain co-morbidities may be overestimated since we relied on patient recall to identify those conditions. Lastly, the use of a 0-10 NRS is not adequate to measure the effect of TV-PBM on quality of life, sexual function, and psychological distress related to pain. Despite these limitations, the data we present reassures us that TV-PBM may potentially be beneficial with a low risk of adverse events.

CONCLUSIONS

In this cohort of women with IC/BPS, TV-PBM was effective in reducing pelvic pain, dysuria, dyspareunia, and pain with exercise. Although the findings of this study are positive, the results should be interpreted with caution as this was an uncontrolled study and the results have not yet been replicated in controlled studies. Additionally, long-term studies will be needed to determine the duration of the therapeutic effect especially when TV-PBM is integrated into a multi-modal treatment regimen.

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