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Comparison of Voiding Dysfunction Phenotypes in Women with Interstitial Cystitis/Bladder Pain and Myofascial Pelvic Pain: Results from the ICEPAC Trial

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Keywords

interstitial cystitis; voiding; uroflow; pelvic pain; visceral pain

Introduction:

Interstitial cystitis/bladder pain syndrome (IC/BPS), a common pelvic pain entity, is characterized by pain or discomfort perceived in the bladder region, often related to bladder fill-state and associated with urinary frequency and urgency. The prevalence of diagnosed IC/BPS in the general population ranges around 1%, while self reported urological bother symptoms, including pain, occur in up to 2.3% of the general population [1]. Infectious, autoimmune, and genetic factors may play a role in the pathogenesis of IC/BPS [2].

The clinical characteristics of IC/BPS themselves suggest that abnormal autonomic nervous system (ANS) control of the bladder could play a significant role in its pathophysiology [3]. For example, changes in sympathetic or parasympathetic tone could account for the observed reduction in functional bladder capacity in IC/BPS and simultaneously enhance pain signaling from bladder afferents [4]. Patients with another pelvic pain disorder, myofascial pelvic pain (MPP), may also harbor voiding dysfunction. However, since this disorder is thought to primarily reflect pelvic floor muscular dysfunction [5], we would expect observed bladder function to reflect this extrinsic somatic muscular abnormality, rather than an intrinsic dysfunction related to the hypothesized changes in autonomic nervous system innervation of the bladder.

ICEPAC (Interstitial Cystitis: Elucidation of Psychophysiological and Autonomic Characteristics) systematically compared autonomic and psychophysiologic characteristics

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of IC/BPS, MPP, and healthy control (HC) subjects [6]. We hypothesized that IC/BPS might harbor specific detrusor or sphincteric contractile voiding abnormalities not present in MPP, whereas MPP would more likely reflect pelvic floor muscle dysfunction such as inability to relax the pelvic floor during voiding. We expected that specific delineation and head-to-head comparison of voiding function might extend our pathophysiologic understanding as well as diagnostic separation of the two disorders in clinic. The purpose of this study is to compare the voiding signature phenotypes and dynamic voiding changes of IC/BPS, IC/BPS+MPP, MPP alone, and HC subjects.

We utilized the uroflowmeter, a practical tool that is often used as a clinical tool to evaluate bladder physiology. Compared to urodynamic studies, it requires no local or general anesthesia, is completely non-invasive, and provides a fairly “physiologic” picture, comparable to daily voiding at home. Uroflow parameters objectively evaluate a patient’s flow pattern, voided volume, maximum flow rate, voiding time, and time to maximum flow [7].

Methods:

The cross-sectional study ICEPAC (IRB 04–09-01 UHCMC; clinicaltrials.gov NCT01616992) enrolled women aged 18–80 years with IC/BPS, MPP, both and HC subjects. Full methodology was published [6]. All subjects had a mean self-assessed pelvic pain score of at least 4 on the numeric rating scale of 0–10 within the past month at the time of enrollment.

IC/BPS required ≥ 6 months of pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as urgency or frequency, with confusable diseases excluded [8]. We additionally required that IC/BPS pain be perceived as linked to bladder filling to reduce the possibility that symptoms attributed to IC/BPS in fact represented MPP. We realized this might reduce our sensitivity (we might miss some patients who in fact had BPS), but would improve our specificity and separation, as the two disorders overlap in many ways [9]. Pelvic tender points (TPs) played no role in this definition. All participants except HC subjects underwent a pelvic floor examination.

MPP required ≥ 3 months non-cyclic chronic pelvic pain unrelated to bladder filling or emptying, with TPs ≥ 4/10 pain numeric rating score in ≥ 2/5 muscles: bilateral levator ani (puborectalis), obturator internus and midline perineum, examined with the index finger applying 2kg of pressure [10]. Participants could meet criteria for both disorders. The variance in pain duration thresholds for qualification of subjects as IC/BPS or MPP, though not optimally comparable, was required for two reasons: (1) these durations reflected the then current definitions in the literature, and (2) subjects with MPP are often diagnosed and treated to near-resolution before six months have elapsed, reducing potential participants.

ICEPAC uncovered a large group of subjects with both IC/BPS and MPP who were grouped as their own phenotype in the analysis. HCs were age-matched to within +/− 3 years of IC/BPS patients and had no evidence of fibromyalgia, chronic fatigue syndrome, IC/BPS, MPP, chronic pain, migraine headache or other putative IC/BPS co-morbid disorder [6].

Patients arrived to the urologic lab with comfortably full bladder (i.e. desire to void) and provide a completed 24-hour voiding diary with bladder pain ratings at each void. In the lab, patients voided in a sitting position in a private setting into a gravimetric uroflowmeter (FloPoint Elite, Verathon, Bothell, WA, USA). Both pre-void volume and post-void residual volume were assessed by bladder ultrasound as we attempted to bring voided volumes to greater than 150cc and less than 300 cc. The results were reported in accordance with the International Continence Society uroflow terminology on flow patterns including: maximum flow-rate (Q_{max}), average flow-rate (Q_{avg}), voided volume (VV), time to peak flow (T Q_{max}), and voiding time (T_{vv}) [9] and analyzed using Graphpad Prism software. Continuous variables are presented as mean and standard error (SE). Groups were compared using one-way ANOVA (with a level of significance $p<0.05$) and Tukey's test (with a level of significance of $p<0.01$).

Results:

The study included 111 patients, 36 HC, 24 with IC/BPS, 14 with MPP, and 37 with both (demographics Table 1). The multimodal pain intensity score (MPI, Fig 1), a measure of overall body pain, not surprisingly, differed between the control group (0.06±0.04) and all pelvic pain groups (3.14±0.31, 4.20±0.21, and 3.47±0.41, for IC/BPS, IC/BPS+MPP, and MPP respectively, $p<0.01$). In addition, IC/BPS differed from IC/BPS+MPP ($p<0.01$). Numeric rating scale (NRS) for pain intensity reflected the response to the question: "on a scale of 0–10 with 0 'no pain' and 10 'worst pain imaginable', how much pain do you have when your bladder is full?" Full bladder NRS differed among all groups (Fig 1). Patients with IC/BPS (with or without MPP) had more bladder pain than patients with MPP, and the presence of MPP further worsened the pain of subjects with IC/BPS.

Based on voiding diaries (Fig 2), subjects with IC/BPS (with or without MPP) showed reduced average voided volume compared to subjects without IC/BPS (HC and MPP alone) and higher 24 hour voiding frequency.

Uroflow (Fig 3) showed reduced average and peak flow rates in all pelvic pain groups, which did not differ from one another. No statistically significant differences occurred among the pelvic pain groups for "time to peak flow", "void duration", or "voided volume." A non-significant pattern of increasing time to peak flow was observed in subjects with MPP, which may require a larger group of subjects to show significance, but supports the concept of difficulty relaxing the pelvic floor.

Discussion:

Two frequently overlapping disorders, IC/BPS and MPP often produce disabling pelvic pain in women. The lack of objective measures aiding in each diagnosis creates challenges and delays in attaining firm diagnoses and treatment. This clinical conundrum has also resulted in mixed data from clinical trials because chronic pelvic pain is heterogeneous. To the best our knowledge, this is the first study to examine voiding parameters in age matched HC and clinically diagnosed females with these two specific syndromes. Our goal was to delineate

differences in the voiding phenotype of these two disorders, and potentially identify additional clues from simple non-invasive testing to improve diagnostic specificity.

The study demonstrates several major findings. First (Fig 1), though patients with IC/BPS (with or without MPP) had similar pain levels to those with MPP alone based on the MPI overall pain level, their pain levels with bladder filling were higher. Furthermore, the combination of MPP to IC/BPS increased both the overall pain levels and the pain specific to bladder filling. Second, patients with IC/BPS (with or without MPP) had significantly lower voiding volumes and higher voiding frequency than both healthy controls and MPP patients despite similar daily fluid intake (Fig 2). Third, flow rates were reduced in all groups compared to HC (fig 3). In addition, though not statistically significant, perhaps related to the small number of MPP subjects, the time to peak flow in MPP subjects appears higher than in other groups, compatible with the known contracted pelvic floor musculature during voiding.

The higher MPI pain scores for IC/BPS, IC/BPS+MPP, and MPP (compared to HC) simply reflect the fact that most pelvic pain disorders also manifest generalized pain[12]. While it was not surprising that the presence of MPP in someone with IC/BPS increased overall pain levels reflected in the MPI, it did come as a surprise that MPP increased bladder pain levels compared to IC/BPS alone (Fig 1, right panel). Perhaps IC/BPS+MPP, rather than simply representing the addition of two disorders, actually constitutes its own separate syndrome. In studies evaluating urodynamic parameters of IC/BPS patients, Sastry and colleagues noted that 73% of IC/BPS patients also exhibited high tone pelvic floor muscle dysfunction, indicating that these symptoms may frequently overlap [12]. Another study showed concomitant pelvic floor muscle dysfunction in over 90% of IC/BPS subjects [13]. Furthermore, subjects with MPP had significantly less pain with a full bladder than subjects with IC/BPS (with or without MPP). This finding supports the concept that MPP does not primarily involve the bladder and its afferents, but rather constitutes a pelvic floor disorder with secondary voiding dysfunction due to bladder outlet obstruction.

Voiding diary analysis support this concept. Patients with IC/BPS (with or without MPP) experienced lower volumes and higher voiding frequencies compared to patients with MPP alone or HC. Sastry and colleagues found similar results using urodynamic evaluation of patients with IC/BPS [12]. Patients with MPP may therefore be able to tolerate higher bladder capacity without activating the detrusor muscle, as others have also found by voiding diary analysis [14], in contrast to patients with IC/BPS whose frequency and urgency matches overactive bladder patients. [15]

Uroflow study results (Fig 3) showed the expected reduction in flow rates for subjects with IC/BPS [12, 16]. The observation that MPP subjects flow rates were indistinguishable from those of IC/BPS subjects implies that this uroflow parameter may not be a useful clinical discriminator. We believe these results are accurate because the voided volumes made as similar as possible by the methodology, as shown in Fig 3E. By definition, these slower rates reflected longer and smaller voids than healthy controls, though these component variables were not statistically significantly different. The uroflow volumes did match the entirely

separately ascertained voiding diary volumes remarkably well (compare Fig 2 first panel and Fig 3 last panel) suggesting robust measures.

Of interest, the time to peak flow in MPP patients was almost twice as high as the time to peak flow in patients with IC/BPS and HC, though not statistically significant, likely related to the small number of MPP subjects. This finding could reflect delay in relaxation in the MPP group, consistent with the known pelvic floor dysfunction that occurs in this disorder. Both the external urethral sphincter and pubococcygeal muscles contribute to voiding dysfunction in women with dysfunctional voiding or urinary retention [17]. If reproducible, this finding could provide a differentiating uroflow signature for these disorders. In contrast, uroflow abnormalities in IC/BPS presumably reflect loss of detrusor power rather than an outflow issue. In this light, the intermediate time to peak flow status of combined IC/BPS +MPP (between essentially normal (IC/BPS and long MPP) may result from less pelvic floor opposition to flow when detrusor pressure is lower.

Combining uroflow measurements/voiding signature phenotypes with the constellation of signs and symptoms used to differentiate MPP and IC/BPS may be a useful aid in differentiating between these disease states and making the appropriate diagnosis. Findings favoring IC/BPS over MPP include: pain with a full bladder, (which may be nearly two-fold that of patients with MPP despite similar MPI scores); lower voiding volumes (patients with IC/BPS exhibited volumes approximately 25% lower than patients with MPP); and higher voiding frequency (voiding frequency in patients with IC/BPS was 15% higher than in patients with MPP). Peak and average flow rates do not provide any differentiating power between IC/BPS and MPP patients. However, a longer time to peak flow may favor MPP if this finding can be confirmed in a larger sample.

The study has several limitations, including already mentioned low sample size of subjects with isolated MPP. Second, the IC/BPS cohort was a bit older though voiding parameters were reassuringly similar, indicating that this probably did not play a significant role in the findings. Third, voiding diary values are open to recall bias, where patients are performing this study on their own then reporting their findings. The similarity of uroflow and voiding diary volumes across the three groups is somewhat reassuring here. Fourth, the uroflow assessment has inherent technical limitations, as variations in urine specific gravity may impact flow rate by up to 3%. This is in addition to the baseline error in the flow rate of 4–15% and volume error of 1–8% [18]. Fifth, these data reflect the clinical picture at a single moment in time, which may have been different if measured at another instance. Sutcliffe and colleagues recently described the disease process in female patients with IC/BPS in one site from the MAPP network and noted that over the course of a year, patients may exhibit worsening of their pelvic pain, with symptom flares lasting more than one day associated with a “global worsening of symptoms” [19]. We do not know if these measurements also change in the same dynamic waxing and waning symptomatic flares with varying clinical presentations [20]. The consistency of our findings within groups is reassuring in this context.

Study strengths include its prospective nature, the comparison of three chronic pelvic pain syndromes, and being the first study to methodically examine their voiding signature

phenotypes. These results add some quantitative data to a generally rather imprecise science underlying the clinical approach to this group of patients.

Conclusion:

This quantitative evaluation of voiding diary and uroflow metrics in chronic pelvic pain patients reveals clues from voiding phenotypes that may aid in the differentiation and diagnosis of pelvic pain syndromes. Peak and average flow rates are similar between IC/BPS and MPP patients. A longer time to peak flow may favor MPP though this finding needs confirmation. Further prospective studies confirming these findings in a larger sample of isolated MPP subjects, assessing stability of findings across time, and better quantitating these changes with full urodynamic studies will further define the differences between these female pelvic pain disorders.

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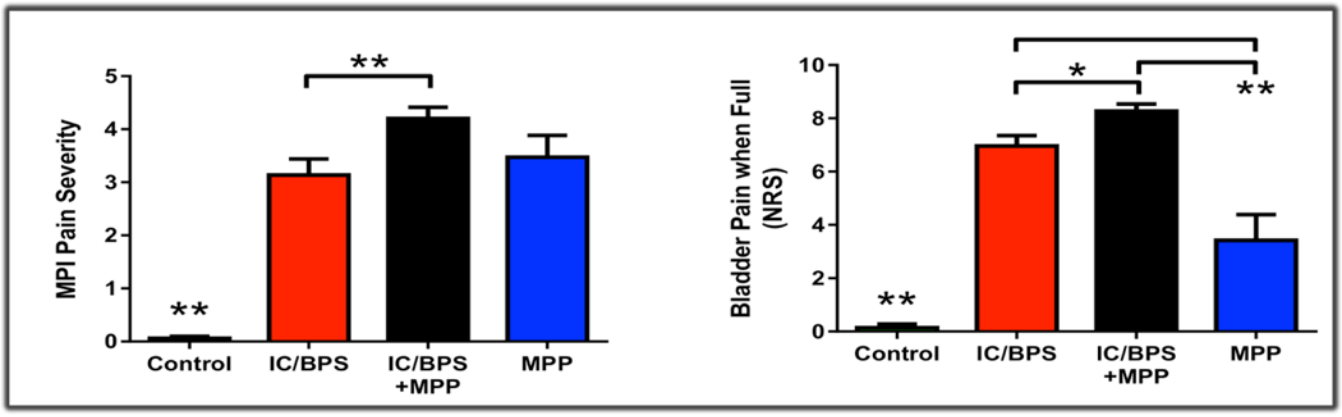

Figure 1.

Pain Measurements. Values depicted are mean ± SE. Comparisons are via one-way ANOVA and Tukeys multiple comparisons. *p<0.05, **p<0.01.

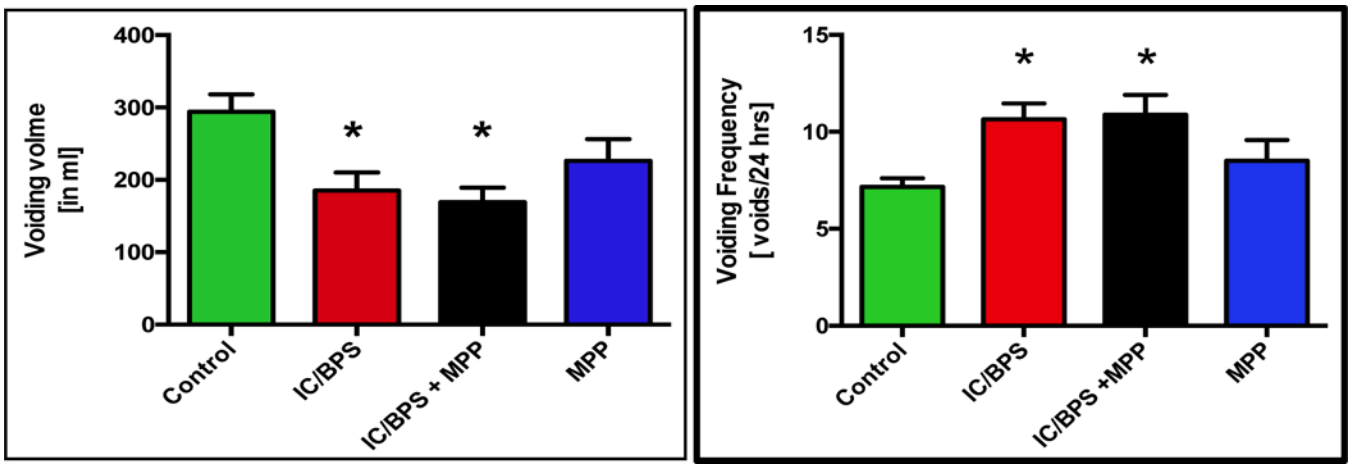

Figure 2.

Voiding diary measurements. Values depicted are mean ± SE. Comparisons are via one-way ANOVA and Tukeys multiple comparisons. *p<0.05, **p<0.01.

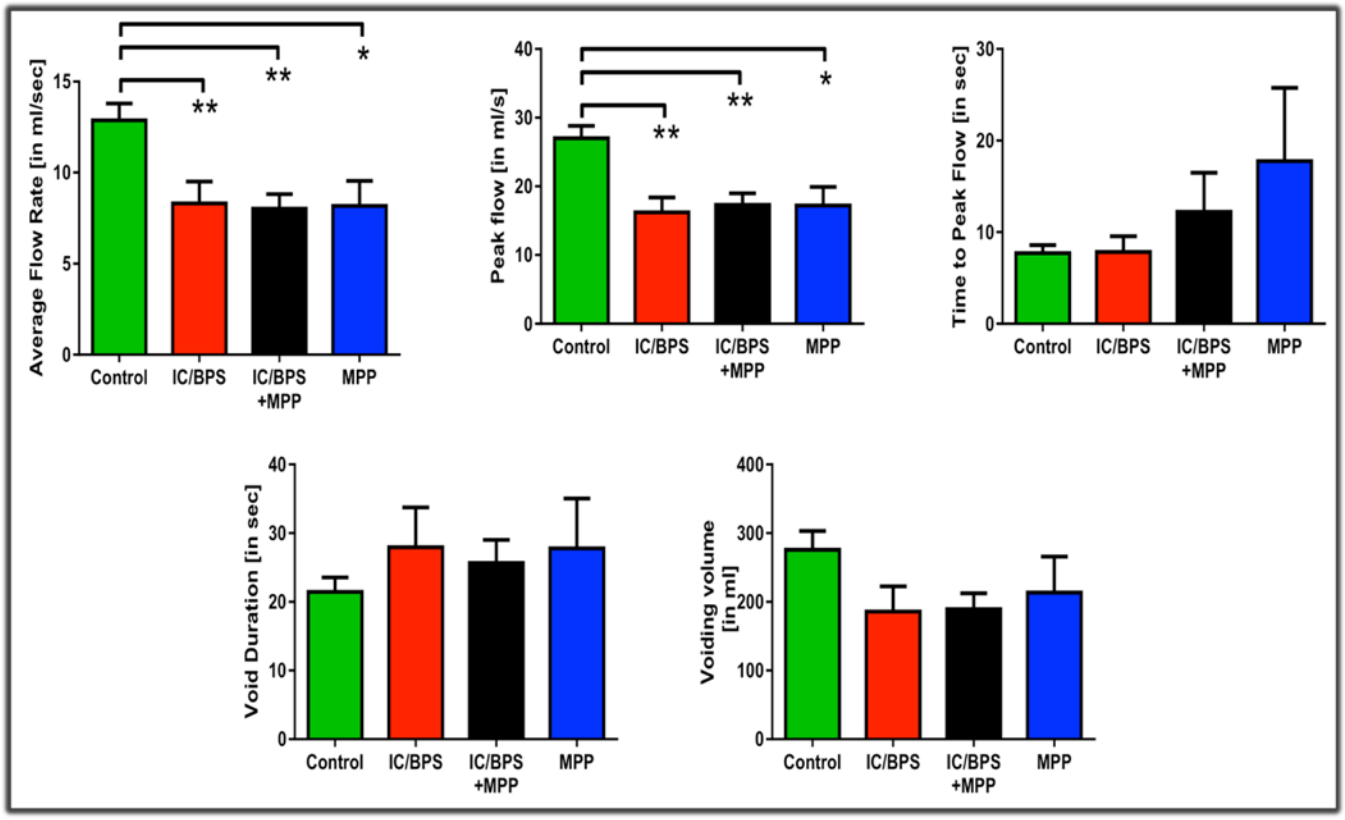

Figure 3.

Uroflow Measurements. A. Average flow rate. B. Peak Flow (QMax). C. Time to Peak Flow. D. Void Duration. E. Voided Volume. All values depicted are mean ± SE. Comparisons are via one-way ANOVA and Tukeys multiple comparisons. *p<0.05, **p<0.01.

Table 1

Demographics

	Healthy Controls (n=36)	IC/BPS (n=24)	IC/BPS +MPP (n=37)	MPP (n=14)
Age, mean (SE)	38.5 (2.5)	47.8 (2.8)	38.6 (2.1)	34.0 (2.9)
Race				
Caucasian	26	23	26	10
African American	5	0	10	4
Other	4	1	1	0
BMI, mean (SE)	26.9 (1.4)	26.9 (1.2)	31.1 (1.5)	32.0 (2.1)