Segmental Hyperalgesia to Mechanical Stimulus in Interstitial Cystitis/Bladder Pain Syndrome: Evidence of Central Sensitization

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Abbreviations and Acronyms

BPS = bladder pain syndrome

DH = dorsal horn

IC = interstitial cystitis

QST = quantitative sensory testing

VAS = visual analog scale

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For another article on a related topic see page 1454.

Editor's Note: This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1480 and 1481.

Purpose: We investigate if subjects with interstitial cystitis/bladder pain syndrome demonstrate mechanical or thermal hyperalgesia, and whether the hyperalgesia is segmental or generalized (global).

Materials and Methods: Ten female subjects with interstitial cystitis/bladder pain syndrome and 10 age matched female controls without comorbid fibromyalgia or narcotic use were recruited for quantitative sensory testing. Using the method of limits, pressure pain and heat pain thresholds were measured. Using the method of fixed stimulus, the visual analog scale pain experienced was recorded when a fixed pressure/temperature was applied.

Results: The visual analog scale pain rated by female subjects with interstitial cystitis/bladder pain syndrome was significantly higher than that rated by female control subjects when a fixed mechanical pressure (2 or 4 kg) was applied to the suprapubic (T11) area ($p = 0.028$). There was an up shift of the stimulus-response curve, which corresponded to the presence of mechanical hyperalgesia in the suprapubic area in interstitial cystitis/bladder pain syndrome. However, the visual analog scale pain rated by subjects with interstitial cystitis/bladder pain syndrome was not different from that rated by controls when a fixed pressure was applied at the other body sites (T1 arm, L4 leg, S2-3 sacral). No difference in visual analog scale pain rating was noted when a fixed heat stimulus (35C or 37C) was applied to any of the body sites tested (T1, T11, L4, S2). There was no difference in pressure pain thresholds or thermal pain thresholds between subjects with interstitial cystitis/bladder pain syndrome and controls.

Conclusions: Female subjects with interstitial cystitis/bladder pain syndrome showed segmental hyperalgesia to mechanical pressure stimulation in the suprapubic area (T10-T12). This segmental hyperalgesia may be explained in part by spinal central sensitization.

Key Words: cystitis, interstitial; hyperalgesia; central nervous system sensitization; pain measurement

Interstitial cystitis/bladder pain syndrome is characterized by hypersensitivity to bladder distention. At any given volume of bladder filling, subjects with IC/BPS reported significantly higher rating of bladder pain on a visual analog scale compared to control subjects without IC/BPS.[1] Although bladder hyperalgesia is a hallmark feature of IC/BPS, it is unclear if patients with IC/BPS have generalized hyperalgesia outside of the pelvis. Previous studies have examined pain thresholds in

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mixed populations of subjects with IC/BPS and did not account for the presence of other comorbid syndromes[2,3] or other variables such as narcotic use. These studies revealed lower pressure pain thresholds compared to controls in sites distant from the bladder[4] and less tolerance to ischemic stimuli but no difference in thermal pain measures.[4,5] Fitzgerald et al showed that the perception thresholds to nonpainful electric current on the skin in subjects with IC/BPS were no different than those in controls in the C5, T6, T10, T12 and S3 dermatomes, and no global differences were present in the warmth perception threshold or vibration perception threshold in the IC/BPS group compared to controls.[1] However, subjects with IC/BPS did report more intense sensations in the T12 and S3 dermatomes when subjected to a sustained suprathreshold thermal stimulus.[6] Overall the reported literature is conflicting with respect to the presence of hyperalgesia in IC/BPS.

Therefore, in this study we investigate 1) if subjects with IC/BPS demonstrate mechanical or thermal hyperalgesia, and 2) whether the hyperalgesia is segmental (more pronounced in T10-T12 or S2-S4) or global (also involving the extremities). To avoid factors known to alter sensory processing, a sample of subjects with IC/BPS was enrolled which was free from the comorbidity of fibromyalgia or from daily narcotic use.

MATERIALS AND METHODS

Subjects

A total of 10 female subjects with a clinical diagnosis of IC/BPS and 10 age matched female healthy volunteers (controls) were recruited for QST. Subjects with IC/BPS had pain, pressure or discomfort perceived to be related to the bladder and/or pelvis in the last 6 months, with associated urinary symptoms such as frequency or urgency.[7] All subjects with IC/BPS underwent a urological evaluation including history and physical examination, and completed questionnaires including the ICSI and ICPI (IC Symptom Index and IC Problem Index),[8] PUF (Pelvic Pain and Urgency/Frequency questionnaire)[9] and GUPI (Genitourinary Pain Index questionnaire).[10] Subjects with a diagnosis of fibromyalgia or those who used narcotic pain medication were specifically excluded from the study. All participants signed an informed consent and were reimbursed for their effort. The study was approved by the institutional review board of Washington University. Subject demographics are listed in the table.

Subject demographics

	Mean ± SEM IC/BPS (range)	Mean ± SEM Controls (range)	p Value
Age	41.4 ± 5.1 (21–68)	39.7 ± 4.6 (22–64)	0.80
ICSI	11.2 ± 1.5 (6–19)	2.9 ± 0.8 (1–9)	0.0001
ICPI	8.9 ± 1.2 (3–14)	1.4 ± 0.7 (0–6)	<0.0001
PUF	17.5 ± 1.8 (6–26)	3.2 ± 0.7 (1–7)	<0.0001
GUPI	22.4 ± 3.0 (4–36)	1.9 ± 0.7 (0–5)	<0.0001

Mechanical Pain Threshold Determination

A handheld pressure algometer with a 1 cm^2 flat probe was used to deliver a steadily increasing and quantifiable pressure to underlying muscle/deep tissues (Algomed, Medoc Ltd, Minneapolis, Minnesota). The method of ascending limits was used.[11] Subjects were instructed to press a button when the first sensation of pressure pain occurred (pressure pain threshold). Subjects underwent a training session before testing. Each body site was stimulated 3 times and the average was calculated. The sites were 1) T1: upper extremity—ulnar surface of the forearm, halfway between the wrist and elbow; 2) T11: suprapubic—midline between the umbilicus and pubic symphysis; 3) L4: lower extremity—medial surface of the leg, halfway between the knee and ankle; 4) S2: sacral dermatome—posterior medial surface of upper thigh and 5) S3: perineum—midline perineum behind the scrotum and anterior to anus in males, behind posterior introitus and anterior to anus in females.

Heat Pain Threshold Determination

A 9 cm^2 Peltier thermode with a flat contact surface (Pathway ATS, Medoc Ltd) was used to deliver increasing heat to the skin (an increase of 1C per second) after the skin was initially habituated at a baseline temperature of 32C. Subjects were given the instruction to "push the button the moment you begin to feel pain" (heat pain threshold). The thermode rapidly returned to the baseline temperature. Each body site was stimulated 3 times and the average was calculated. The same 4 sites previously described were tested. Due to concern of genital burn the perineum site (S3) was not heated.

VAS Pain Rating During Fixed Intensity Stimulus Testing

Since the anticipation of a predictable stimulus of increasing intensity (method of ascending limits) may bias the pain threshold reporting in some subjects with IC/BPS (eg those with anxiety, hypervigilance or catastrophizing),[12] we also applied a random sequence of fixed intensity stimulus (2 or 4 kg, 35C or 37C) to the body sites (method of constant stimulus). Immediately after the stimulus was applied the subjects were asked to rate the pain severity on a sliding ruler with a VAS from 0—no pain to 10—worst pain. The averages of 3 VAS ratings were used.

Statistics

Pressure pain thresholds and heat pain thresholds (dependent variables in figure 1) were compared independently using 2-tailed t-tests at each of the body sites to look for patient group effects (factor was IC/BPS vs controls). Post hoc Mann-Whitney tests were performed. VAS pain ratings (dependent variables in figure 2) at each of the body sites were compared using 2-factor ANOVA. The 2 factors were patient groups (IC/BPS vs controls) and stimulus intensity (2 vs 4 kg, or 35C vs 37C). Interactions