Phenotypically Directed Multimodal Therapy for Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective Study Using UPOINT

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OBJECTIVES Large, controlled trials in chronic pelvic pain syndrome (CPPS) have failed due to patient heterogeneity. To phenotype CPPS patients, we developed the UPOINT system with 6 domains (Urinary, Psychosocial, Organ-Specific, Infection, Neurologic/Systemic and Tenderness). In this study, we treated patients with multimodal therapy based on the UPOINT phenotype and measured response after at least 6 months.

METHODS Patients with CPPS were offered multimodal therapy based on the UPOINT phenotype (eg, Urinary: alpha blocker or antimuscarinic; Organ-specific: quercetin; Tenderness: physical therapy). One hundred patients agreed to therapy and were reexamined after 26 weeks. Primary endpoint was a minimum 6-point drop in NIH-Chronic Prostatitis Symptom Index (CPSI).

RESULTS Mean age was 46 years, and median symptom duration was 24 months. A median of 3 UPOINT domains were positive, the most common being Organ-specific (70%), Tenderness (64%), and Urinary (59%). With a median 50-week follow-up, 84% had at least a 6-point fall in CPSI. Number of domains and initial CPSI did not predict response. Mean changes (± SD) for CPSI subscores were pain 11.5 ± 3.2 to 6.1 ± 3.9, urine 4.7 ± 3.1 to 2.6 ± 2.0, QOL 9.1 ± 2.3 to 4.5 ± 2.8, and total 25.2 ± 6.1 to 13.2 ± 7.2 (all $P < .0001$). No domain predicted outcome; however, quercetin use resulted in a greater CPSI decrease.

CONCLUSIONS Multimodal therapy using UPOINT leads to significant improvement in symptoms and quality of life. Moreover, a placebo-controlled trial for every therapy combination is not feasible, and results using UPOINT compare favorably with all large trials of monotherapy. UROLOGY 75: 1249–1253, 2010. © 2010 Elsevier Inc.

National Institutes of Health (NIH) category III prostatitis, also known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common condition with significant impact on quality of life.[1] This clinically defined syndrome has a multifactorial etiology and seems to respond best to multimodal therapy.[2] Although numerous single-center or small studies have shown efficacy for the condition, large multicenter trials of promising treatments have often shown minimal or no benefit when compared with placebo.[3] There are multiple potential explanations for the failure of these studies including patient selection, incorrect treatment choice, dose and duration of therapy, and incorrect primary endpoints. A likely explanation, however, is that the heterogeneous nature of patients in these studies may have prevented an intervention with a single etiologically-based mechanism to obtain a positive outcome. This would be analogous to testing an effective migraine drug in patients only defined as having a headache, which could include patients with a tension headache, brain tumor, infected tooth, or neck spasm. Currently, we do not have validated biomarkers that would allow us to classify patients in a way that could guide therapy.

We have proposed a 6-point clinical phenotyping system to classify patients with urological chronic pelvic pain and subsequently direct appropriate therapy.[4] The clinical domains are Urinary symptoms, Psychosocial dysfunction, Organ-specific findings, Infection, Neurologic/Systemic, and Tenderness of muscles. This produces the mnemonic UPOINT. Each domain is clinically defined, linked to specific mechanisms of symptom production or propagation, and associated with specific therapy. We have previously shown that number of UPOINT domains is associated with symptom duration and severity in both CP/CPPS[5] and interstitial cystitis.[6] Others have confirmed a correlation between the NIH Chronic Prostatitis Symptom Index (CPSI) and number of UPOINT domains in CPPS.[7] It is our hypothesis that such clinical phenotyping can lead to better patient stratification for therapy. Here we report on the results of multimodal therapy selected according to UPOINT in men with CPPS.

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MATERIAL AND METHODS

We reviewed the clinical records of new patients with a diagnosis of CPPS seen at the Cleveland Clinic between March 2008 and April 2009, by 1 physician whose information was recorded in an institutional review board–approved database. Of 186 charts reviewed, 100 met criteria for follow-up and data, as stated below. Each patient had symptom severity measured by the NIH CPSI,[8] reported as subscores for pain (0-21), urinary (0-10), and quality of life (0-12), as well as a total score (0-43). Review of the history, physical, cultures of urine, and expressed prostatic secretions or post-massage urine results led to a yes/no classification for each of the 6 UPOINT domains as previously described.[4] Briefly, Urinary was positive if the patient had bothersome urinary symptoms or high post-void residual. Psychosocial was positive in the presence of clinical depression or catastrophizing. Organ-specific was positive if there was specific prostate tenderness on examination, leukocytosis on microscopic examination of prostatic fluid or VB3, or presence of hematospermia. Infection was positive (in the absence of a current or previous urinary tract infection) if gram-negative bacilli or *Enterococcus* localized to prostatic fluid or if urine was positive for Ureaplasma. Neurologic/Systemic was positive if there was pain outside the abdomen and pelvis or from the concurrent diagnoses of fibromyalgia, chronic fatigue syndrome, or irritable bowel syndrome. Finally, Tenderness was positive if there was palpable muscle spasm or trigger points in abdomen or pelvic floor. Criteria for inclusion was complete information on CPSI and UPOINT phenotype, patient agreement to follow the treatment plan, and a follow-up evaluation at least 6 months after the initial appointment. The primary endpoint for clinical improvement was a decrease of at least 6 points in total CPSI score[9] as measured at the most recent follow-up. Secondary endpoints included a decrease of total CPSI of at least 25% or 50% (which has been associated with moderate and major improvement in previous studies),[10] mean change in total CPSI, and the urinary and quality of life subscores before and after therapy.

Patients were offered therapy based on each positive phenotype. For the urinary phenotype, patients were treated with alfuzosin[11] (45 patients), tolterodine (8 patients), or both (3 patients) depending on symptoms and previous therapy. For Psychosocial, patients were referred to a psychiatrist or psychologist for management of depression or stress if they desired (10 of 37 patients). For Organ-specific, patients were treated with quercetin 500 mg bid[10] (64 patients). They were recommended to use a form of quercetin without vitamin C (to avoid urinary acidification) that included bromelain and papain to improve absorption (such as Prosta-Q, Farr Laboratories, Santa Monica, CA). For Infection, patients were treated with culture-specific antibiotics (2 patients), or in the case of a positive ureaplasma test, with clarithromycin (500 mg bid for 10 days) (13 patients). Patients with the Neurologic/Systemic domain were treated with amitriptyline (25 patients)[12] (starting at 10 mg/d, increasing to 50 mg/d as needed) or pregabalin (9 patients)[13] (starting at 75 mg bid up to 150 mg bid). Patients identified with skeletal muscle Tenderness were treated with pelvic floor physical therapy/myofascial release (59 patients).[14]

Statistical analysis used GraphPad Prism 4.0. Association between domain and treatment numbers with categorical outcome were made with the chi-square test. Before and after CPSI scores were analyzed with a paired *t*-test and changes in score by domain or treatment by the unpaired *t* test. Symptom duration was not normally distributed, and therefore effect of duration on treatment outcome was compared by the Mann-Whitney *U* test. Correlations between continuous and categorical values were assessed by the Spearman r correlation coefficient. Statistical significance was set at an alpha of 0.05. Based on previous standard deviation and range of CPSI values in these patients,[15] the calculated power of the study was an 80% probability to detect a drop of 1.2 points in total CPSI.

RESULTS

Mean age was 46 years (range 18-71), and median symptom duration before the initial visit was 24 months (range, 3-380). The number (and thus percentage, given an N of 100) of men with each individual phenotype was Urinary 59, Psychosocial 37, Organ-specific 70, Infection 16, Neuromuscular/Systemic 39, and Tenderness of muscles 64. The number of patients having positive domains was 6 for 1 domain, 31 for 2 domains, 41 for 3 domains, 16 for 4 domains, and 6 for 5 domains (no patient had zero or 6 positive domains). Only 7 patients had 1 therapy, 45 had 2 therapies, 38 had 3 therapies, and 8 had 4 therapies.

Overall, 84 patients achieved the primary endpoint of a 6-point or greater improvement in total CPSI. The chance of reaching the primary endpoint was not significantly different regardless of number of positive domains (1 domain 100%, 2 domains 94%, 3 domains 80%, 4 domains 75%, 5 domains 83%, $P = .89$ by chi-square test). Fifty-one patients had a 50% or greater improvement in total CPSI, whereas 84 patients had at least a 25% or greater improvement. As seen in Fig. 1, there was a difference between domain numbers and chance of falling into the 3 outcome categories (>50%, 25%-50%, or <25%); however, the 2 groups with

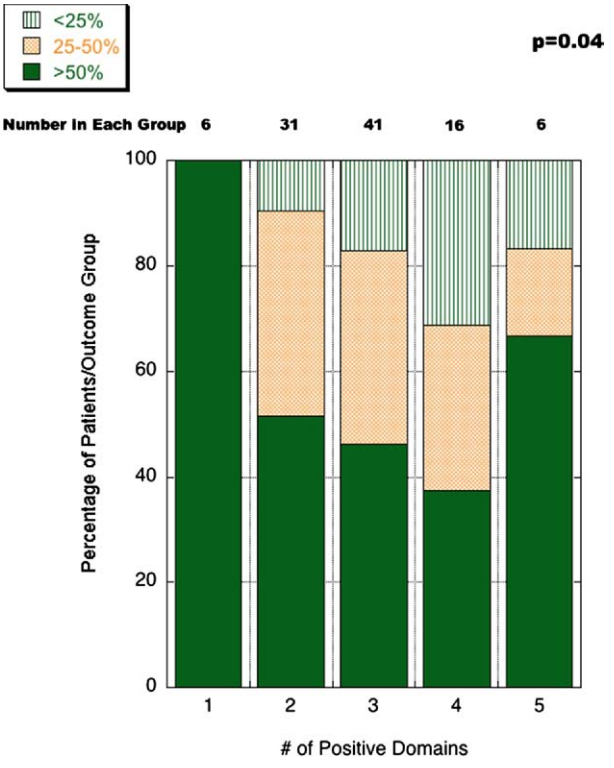

Figure 1. Proportion of patients achieving each outcome level according to number of positive UPOINT domains.

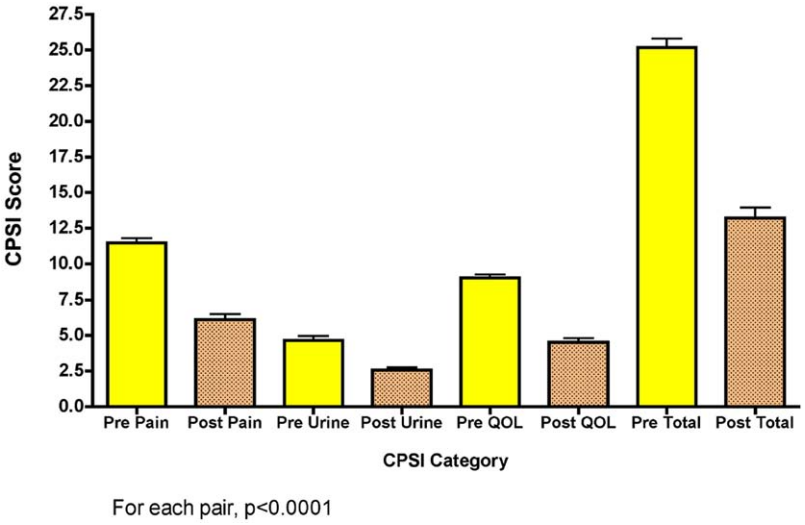

Figure 2. Change in CPSI subscores and total score before and after therapy.

the highest improvement at the 50% level were 1 and 5 positive domains ($P = .04$ by chi-square test). One explanation for better improvement with higher domain number could be that simply having more concurrent therapies improves outcome. When comparing outcomes by numbers of treatment, there was no difference whether measured by the primary ($P = .92$) or secondary ($P = .34$) outcomes. As seen in Fig. 2, mean changes for all CPSI subscores were significantly improved from baseline: Pain 11.5 ± 3.2 to 6.1 ± 3.9, Urine 4.7 ± 3.1 to 2.6 ± 2.0, QOL 9.1 ± 2.3 to 4.5 ± 2.8, and Total 25.2 ± 6.1 to 13.2 ± 7.2 (all $P < .0001$ by paired *t*-test).

As we found in our previous study,[5] the number of UPOINT domains correlated with the initial CPSI (Spearman $r = .47$, $P < .0001$). The improvement seen in all groups cannot simply be attributed to regression to the mean of more symptomatic patients, because number of UPOINT domains did not correlate with drop in CPSI (Spearman $r = .034$, $P = .74$). In addition, drop in CPSI did not correlate with symptom duration or number of therapies ($P = .86$ and $P = .63$, respectively). Furthermore, there was no correlation between CPSI drop and the difference between number of UPOINT domains and number of therapies ($P = .63$). As seen in Fig. 3A, no domain was associated with a significantly lower improvement in CPSI and the only domain associated with a greater CPSI improvement was Organ-specific. This was probably because of the linkage of Organ-specific with quercetin therapy, which was the only therapy associated with a significantly greater symptom improvement (Fig. 3B).

COMMENT

A population of men diagnosed with CPPS comprise a heterogeneous mix of patients with diverse etiologies and different responses to therapies. Currently, no biomarkers are validated to help guide classification and treatment. Our approach to this clinical dilemma was to propose a clinical phenotype classification in an attempt to better stratify CPPS patients according to likely etiologic mechanisms.[4] Each domain is defined by clinical parameters, and each is associated with domain-specific treatments. We have shown in a retrospective analysis that there is a diversity of phenotypes in a typical patient population and patients with more positive domains have worse symptom severity,[5] an observation confirmed by others in CPPS[7] and interstitial cystitis.[6] Although correlating UPOINT domains with patient features such as symptom duration, specific symptoms, and symptom severity can generate hypotheses on etiologic mechanisms, its intended purpose was to improve clinical outcomes by guiding therapy.

The current state of evidence-based therapy for CPPS is in flux.[3] Numerous therapies have shown promise in small, single-center studies but then failed in larger multicenter studies. For example, numerous studies have shown the benefit of alpha blockers for the voiding symptoms of CPPS and also raised the question whether pain was improved as well.[16] A well-designed, properly powered NIH-sponsored study comparing alfusozin to placebo failed to show a difference in symptom improvement, but included men who did not have voiding symptoms,[11] as did a study of antibiotics and tamsulosin.[17] The question is therefore raised whether alpha blockers are of no benefit in CPPS or whether they would have benefit, possibly as one of several concurrent therapies, used only in men with voiding symptoms. Indeed, multimodal therapy does appear superior to single therapies in CPPS[15] and men with CPPS often have systemic complaints,[18] psychological catastrophizing[19] and pelvic floor tenderness,[20] none of which could be expected to improve with prostate- or bladder-targeted therapies.

In this study, we report on symptom improvement using multimodal therapy for CPPS, selected on the basis of the UPOINT phenotype. Overall, 84% of men had

Figure 3. (A) Improvement of total CPSI by the presence or absence of each UPOINT domain. U = Urinary symptoms; P = Psychosocial dysfunction; O = Organ-specific findings; I = Infection; N = Neurologic/Systemic; T = Tenderness of muscles. **(B)** Improvement of total CPSI by the use of each individual therapy. Y = Yes; N = No; alpha = alpha blocker; Phyto = phytotherapy; Neuro = neuroleptic; PT = physical therapy; Ab. = antibiotic.

significant improvement (minimum 6-point drop in total CPSI) at a minimum of 6 months and median of almost 1 year, and 51% had a drop of 50% or more in symptoms. Although there was no direct control group for comparison, we can compare the magnitude of effect with cohort studies, control groups, and treatment groups of multimodal therapy. In the Chronic Prostatitis Collaborative Research Network study of 488 men with CPPS, symptoms were reported as significantly improved at 1 year (with best local therapy) in 17%.[21] In a placebo-controlled trial of finasteride in CPPS, 44% of men had at least moderate improvement at 6 months.[22] In a study of sequential multimodal therapy, which did include both category II and III patients, 80% of patients had at least moderate improvement in symptoms at a minimum of 6 months.[15] In shorter placebo-controlled studies, 70.6% of men treated with cernilton had a minimum 6-point improvement in CPSI at 12 weeks,[23] and 67% of men treated with quercetin had a minimum 25% improvement in CPSI at 4 weeks. Therefore, the results in the present report compare favorably with other single or multitherapy studies to date.

There are limitations to a multimodal observational study that we fully recognize could have influenced the results in either direction. We have a large out-of-town patient population, and therefore patients who did not return for follow-up may have either been completely better or failed therapy and gone elsewhere. As a tertiary referral center, patients typically have longer duration and more severe symptoms, which could influence results through regression to the mean. Nevertheless, we showed no correlation between symptom severity or number of domains and having a positive outcome. Dosage of individual drugs was not standard and titrated to effect and positive and negative interactions could not be individually examined. As an unblinded study, a placebo effect was not controlled for, which could increase response rates. The UPOINT classification itself is in its first version, and criteria for each domain are not fully validated. Finally, it is not known whether simply treating all patients with all the therapies listed would not have an equivalent or superior result.

We did not find that outcome was largely influenced by specific domains, specific therapies, or number of therapies. The only exception was quercetin, whose use (in patients with the Organ-specific domain) resulted in a significantly greater drop in symptoms. Although this may have been coincidental, quercetin does have multiple mechanisms of action that could be effective for different domains. It is an anti-inflammatory and reduces inflammation within the prostate.[24] It is an antioxidant,[25] which may be helpful for pain from ischemic muscle in spasm.[26] Finally, it has antibacterial[27] and antifungal properties.[28]

In conclusion, we have shown in a cohort of 100 CPPS patients that multimodal therapy directed by their UPOINT phenotype resulted in excellent long-term results. Although these results need to be confirmed in a multicenter and placebo or sham-controlled trial, the simplicity of the treatment algorithm makes it attractive as an alternative approach to the current status quo of empiric sequential monotherapy.

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