

Therapeutic Options for Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Chronic prostatitis/chronic pelvic pain syndrome continues to pose a treatment challenge for urologists. Most commonly prescribed medications, such as antibiotics, α -blockers, androgen inhibitors, and anti-inflammatory agents, have been shown to help some patients. However, the efficacy and durability of such treatments lack consistency among men suffering from this disorder. The rationale for such treatments is described in this article, along with possible explanations for the apparent shortcomings. Also included is a brief summary of alternative therapies, which are growing in popularity among patients and gaining acceptance in our medical communities.

Introduction

In the United States, approximately 2 million office visits per year are made because of symptoms ascribed to prostatitis. The most common form of this diagnosis is chronic (abacterial) prostatitis/chronic pelvic pain syndrome (CP/CPPS). The cost of evaluation and treatment is estimated to be 1.5 times greater than controls, which were observed within a health maintenance organization [1]. Surprisingly, most of the differences in cost were due to expenses in health care use, which were unrelated to urology and, more specifically, to their prostatitis diagnosis. This may be indicative of the multifactorial etiology or syndrome.

Although a consensus for evaluation has been established, a treatment algorithm for patients with CPPS remains undefined [2]. Treatments have included antimicrobials, α -blockers, analgesics, skeletal muscle relaxants, phytotherapy, repeated prostate massage, sitz baths, psychotherapy, physical therapy, and biofeedback. Dissatisfaction continues to plague the caregiver and patient with regard to treatment options. Monotherapy, even

when prescribed in a conscientious sequential application algorithm, as documented by Nickel *et al.* [3••], leads to less than satisfying results. In this very well-done observational study, only 19% of the patients were found to have had clinically significant improvement, leading the investigators to conclude that monotherapy may be unsuitable for a large proportion of patients suffering from CP/CPPS.

This author summarizes nonsurgical therapeutic options including antibiotics, α -blockers, androgens, anti-inflammatory agents, and alternative therapies. One must bear in mind that the accepted inclusion criteria for most treatment trials fail to stratify patients in a more thorough fashion, frequently neglecting psychosocial, musculoskeletal, and neuroendocrine factors. For this reason, it may be that there seems to be a consistently significant proportion of patients who do not benefit from these therapies.

Antimicrobials

As documented from the 1998 meeting of the International Prostatitis Collaborative Network [4], antibiotics were the most commonly prescribed treatment for men suffering from CP/CPPS. However, it is widely known and accepted that fewer than 10% of patients have any bacteria localized to the prostate gland, opposing the theory of an infectious etiology. Indeed, it has been shown further that bacterial localization does not correlate with symptomology, nor is the prevalence of bacterial localization distinguishable between CP/CPPS patients and age-matched control subjects [5].

Nickel *et al.* [6] showed that a 6-week course of levofloxacin afforded no greater benefit than placebo. A total of 80 patients were randomized to levofloxacin versus placebo over a 6-week period. After treatment, they were observed again at 12 weeks. Both groups showed progressive improvement, although there was no statistically significant difference at 6 weeks or later. Likewise, there was little difference in the global assessment. No comparisons were made with regard to physical examination or characteristics of the expressed prostate secretions.

In a study comparing antibiotics with α -blockers, investigators randomized 196 patients into three groups: ciprofloxacin, flomax, and placebo. Patients had an

initial National Institutes of Health (NIH)-Chronic Prostatitis Symptom Index (CPSI) of at least 15 and a mean duration of symptoms of 6.2 years. Patients were evaluated after a 6-week treatment period and again at 12 weeks. The modest decrease in CPSI for all of the groups was comparable. After 12 weeks, there was no significant change from the 6- to 12-week interval. The investigators concluded that none of the treatments showed significant benefit among a wide range of secondary outcomes related to symptoms and quality of life [7].

In a review of antimicrobial treatment for prostatitis, Wagenlehner and Naber [8] think that antimicrobial therapy *ex juvantibus* is justified. They recommend an oral fluoroquinolone over a 2- to 4-week period, with reassessment of the patient during that time period. This author recommends the contrary. Antibiotics should be withheld until appropriate cultures have been completed, with reassessment of the patient in 2 to 4 weeks. This is justified because most patients present without fever, retention, or abnormal urinalysis. Avoidance of empiric antibiotic therapy, which has very little compelling evidence, perhaps may decrease the perpetuation of antibiotic overuse, which is so prevalent in this population.

α -Adrenergic Antagonists

The introduction of α -blockers for the treatment of benign prostatic hyperplasia (BPH) afforded significant benefit to these patients, providing a safe and effective nonsurgical treatment. Because some prostatitis patients share similar lower urinary tract symptoms, it would be considered highly plausible that patients with CP/CPPS could benefit as well. Because of the promising results of previously small or uncontrolled trials, more recent investigators have conducted randomized, placebo-controlled trials. One such study randomized 60 patients with CP/CPPS to doxazosin or placebo. The doxazosin was titrated from 1 to 4 mg during the initial 2 weeks of the 3-month trial. The investigators used the International Prostate Symptom Score, a pain scale, and a quality-of-life survey to evaluate the patients. Improvement in all of the parameters was significantly greater in the doxazosin-treated group. The International Prostate Symptom Score improved by 32%, pain by 36%, and quality of life by 36%, while the placebo group improved by 5%, 2%, and 1.5%, respectively [9]. Durability beyond 3 months of therapy was not assessed, nor were other physical parameters such as expressed prostatic secretions.

Gül *et al.* [10] compared 39 patients taking 2 mg of terazosin with 30 patients taking placebo. The patients were compared using the Prostatitis Symptom Score Index (PSSI). The mean pre- and post-PSSI in the treatment group was 9.61 and 6.25, respectively. In the placebo group, the mean PSSI decreased from 9.27 to 8.81. The differences between pre- and post-treatment scores in the terazosin group were statistically significant ($P = 0.002$)

and the difference between the post-treatment score in both groups also was significant ($P = 0.001$). The authors concluded that the favorable response is attributed to smooth muscle relaxation, which would prevent intraprostatic urinary reflux and pain due to spasm [10].

Mehik *et al.* [11] compared alfuzosin 5 mg with placebo and controlled standards. There were 17, 20, and 29 patients in each arm, respectively. The treatment lasted for 6 months with observation at baseline, 6 months, and again at 12 months. Patients were evaluated using the CPSI. A decrease or improvement in score was noted in each group, with varying significance. CPSI change was -9.9, -3.8, and -4.3, respectively. The favorable response in the alfuzosin group, as indicated by the decrease in score, was statistically significant when compared with the two other groups ($P = 0.01$).

Reassessment of the patients 6 months after discontinuation of therapy revealed deterioration in the improved symptoms score, supporting the clinical benefits of this medication.

A subsequent randomized, double-blinded trial using tamsulosin demonstrated superior efficacy of the medication in patients with more severe symptoms. Patients with a CPSI scores in the 75th percentile at baseline enjoyed a greater decrease in their symptom score than average. At the 25th percentile, difference in score was not statistically significant [12]. Although this study was short, it indicated that the treatment required a greater duration to appreciate efficacy. In other words, 2 weeks would be insufficient for reassessment of the efficacy of empiric α -blockade.

Androgens

In rat models, early castration has been shown to improve thymic function, which in turn decreases the development of autoimmune prostatitis [13]. Testosterone and estrogen have been shown to be protective against inflammation. This effect can be blocked by bromocriptine (implicating prolactin in the inflammatory response).

Seo *et al.* [14] studied the effects of hormones and antibiotics in rats with induced chronic bacterial prostatitis. A control group of rats were compared with those who received castration, finasteride, estrogen, or levofloxacin. This study was conducted over a period of 4 weeks. Rats that were castrated and rats that received estrogen had comparable responses to therapy; however, these were not statistically significantly better than controls. The rats treated with finasteride (a type-2 5 α reductase inhibitor) and levofloxacin showed statistically significant improvements when compared with control subjects with regard to eradication of the bacteria and no histologic evidence of prostatic inflammation ($P < 0.05$). The investigators concluded that a decrease in dihydrotestosterone levels leads to decreased prostatic epithelial proliferation and regression of prostatic gland-

dular tissue. Finasteride may enhance therapies targeting chronic bacterial prostatitis; however, the mechanism by which this medication may work in patients remains unclear [14].

Mepartricin, which is a polygenic macrolide that links with estrogens, facilitating their fecal excretion, was studied in men with CPPS. Thirteen subjects received mepartricin 40 mg daily and 13 subjects received placebo over a 60-day treatment period. The CPSI was used to evaluate the patients before and after treatment. A statistically significant decrease in pain was observed within the treatment group. Likewise, quality of life was influenced more favorably among the treated patients; however, there was no significant difference in change of urinary function. The measurement of luteinizing hormone, follicle-stimulating hormone, and testosterone values were similar for both groups before and after treatment. The measurement of 17- β -estradiol levels was significantly lower in the mepartricin-treated group at the end of the study [15]. This medication has been used for the treatment of BPH in some European countries. The rationale for use of this medication for CPPS patients is based on the assumption that abnormal levels of estrogen and androgens may play a role in the symptomology. The authors propose that increased estrogen is associated with increased pain due to stromal alterations and fibromuscular proliferation. It also is thought that estrogen has an early permissive role in the development of prostatitis.

Nickel *et al.* [16] studied the effects of finasteride for the treatment of men with CPPS (Category IIIA-Inflammatory). Sixty-four patients were randomized to receive finasteride 5 mg daily or placebo over a 6-month treatment period. The patients were evaluated and compared using the subjective overall assessment (SOA) and the CPSI. At 6 months, 16% of the placebo group had a greater than 25% decrease in the CPSI compared with 33% in the finasteride group. The SOA improved to a greater degree in the finasteride group. However, the improvements in CPSI and SOA were not statistically significant. However, it is surprising that these investigators did not include the evaluation of the EPS following treatment because the purpose of the study was to evaluate patients with CPPS of the inflammatory subtype.

It may be considered reasonable to try this medication for this patient population given the efficacy of 5 α reductase inhibitors in the treatment of BPH, terminal hematuria, and perhaps prostate cancer prevention. It may influence the inflammatory response of glandular tissue or, by decreasing prostatic volume, decrease the intraprostatic tissue pressure, which has been observed to be elevated in this patient population [17]. However, because prostatic abnormalities have not been proven to be the cause for CPPS, finasteride may have a more appropriate application for the treatment of NIH Category II-prostatitis/chronic bacterial prostatitis.

Anti-inflammatory Therapy

Indices used to study the inflammatory response of the prostate gland include measurement of leukocytes in EPS or semen, cytokines, reactive oxygen species (ROS), and blood flow. Several studies have shown that the white blood cell count measured in EPS, post-prostate massage urine, or semen is unreliable because it cannot be correlated with exacerbations or improvements in symptoms of CPPS. A significant proportion of asymptomatic men have unequivocally positive findings in EPS [18]. Elevated levels of certain cytokines have been observed in patients with CPPS, but to a greater degree in Category IIIA than in Category IIIB. Although interleukin-8, epithelial neutrophil-activating factor-78, and interleukin-1 β have been measured at higher levels in patients with Category-IIIA disease, other investigators have noted that there is no correlation between interleukin-1 β or tumor necrosis factor- α and the white blood cell counts in any of the prostatic specimens [13]. Hochreiter *et al.* [19] found a correlation between cytokine levels in the EPS and changes in patient's symptomology. In the absence of antimicrobial therapy, 80% of patients showed an increase in cytokine levels when symptoms developed and a substantial decrease in cytokine levels when symptoms resolved. Unfortunately, there are no studies looking at the measurement of cytokines before and after treatment with non-steroidal anti-inflammatory drugs.

Elevated levels of ROS or free radicals have been observed in patients with CPPS. In a study by Shahed and Shoskes [20], Category-IIIA patients had significantly higher oxidative stress levels than did Category-IIIB patients. Lower levels were measured in the EPS after treatment with an oral antibiotic or an antioxidant (quercetin). Using colored Doppler ultrasonography, marked increases in blood flow to the prostatic capsule was observed in Category-IIIA and IIIB patients when compared with control subjects. Forms of neurogenically mediated inflammation also have been proposed as a cause for CPPS and other related ailments such as interstitial cystitis [21]. Other observations may support this theory, such as the evidence for abnormal external urinary sphincter function, which is very prevalent in this patient population. Pontari [13] also found corroborative evidence in the observation of similarly abnormal semen parameters and ROS levels in patients with spinal cord injuries and men with CPPS.

There has been only one randomized, double-blind, placebo-controlled trial using an anti-inflammatory medication for patients with CPPS. Rofecoxib, which is no longer on the market, is a cyclooxygenase-2 inhibitor; 161 patients were randomized to treatment with rofecoxib 50 or 25 mg or placebo. The CPSI and global assessment were used to evaluate the patients. The 50-mg dose of rofecoxib was favored over placebo. The CPSI decreased from baseline in all of the groups. Although the main scores numerically favored the rofecoxib groups, the difference was not statistically significant among the groups.

Chronic pelvic pain syndrome is associated frequently with other musculoskeletal dysfunction such as myofascial pain syndromes. Therefore, brief adjunctive therapy, in the form of nonsteroidal anti-inflammatory drugs, would be appropriate.

Alternative Therapies

A growing number of patients in the United States are turning to alternative therapies for a wide range of medical diagnoses. However, many such therapies may be considered conventional or perhaps even mainstream in other settings. For example, phytotherapy or herbal remedies sometimes are the treatment of choice for chronic conditions in Europe and Asia. Acupuncture, with its roots in traditional Chinese medicine, may be the earliest form of neuromodulation.

In a 6-month open-label trial using cernilton, a bee pollen extract, some patients showed a remarkable response. In 72 of 90 patients treated, 36% were cured of their symptoms, while 42% reported significant improvement. Quercetin, a bioflavonoid found in red wine, green tea, and onions, was tested in a prospective, double-blind, placebo-controlled trial that continued for 4 weeks. The CPSI was used to evaluate and compare patients' responses. Decrease or improvement in the CPSI score was statistically significant ($P = 0.003$). In a subsequent study, quercetin was combined with bromelain and papain for presumed enhanced digestive absorption. In this group, there was a greater proportion of patients who experienced significant relief. Saw palmetto is the most commonly used phytotherapy for BPH and lower urinary tract symptoms. This herbal remedy is not known to cause any significant adverse effects. However, there have been no studies regarding its use specifically for patients with CPPS [22].

Chen and Nickel [23] undertook a pilot study to determine whether acupuncture improved the symptoms of patients suffering from CP/CPPS. Twelve patients underwent 6 weeks of acupuncture, administered twice weekly. The CPSI decreased from a mean of 23.2 to 7.5. At the end of therapy, 92% of the patients were responders and experienced more than a 50% decrease in baseline total CPSI. Several plausible theories for efficacy of such treatment include the correction of a neuroanatomic imbalance, historically considered Yin and Yang, analogous to parasympathetic and sympathetic autonomic nervous systems imbalances. Another mechanism of action may result from a stimulatory cascade induced by acupuncture, leading to the suppression of substance P release from the afferent pain terminals. Elevated substance P in the cerebrospinal fluid has been associated with lower pain thresholds and other functional systematic syndromes such as fibromyalgia [24]. In addition, serotonin and its metabolite were found to

be elevated in the cerebrospinal fluid following acupuncture. The serotonergic pathways have been implicated in pain control and bladder function.

Although physical therapy and multidisciplinary approaches may be considered as alternative therapies, their application in patients suffering from CPPS has not been considered part of conventional treatment. Anderson [25] adheres to a very careful genitourinary examination, which includes a mapping of painful trigger points in the patients' abdomen, groin, and pelvic floor. Electromyography also is used for evaluation and subsequent biofeedback treatment. Myofascial trigger point release or soft tissue mobilization is prescribed to patients with findings consistent of hyperirritable spots, taught bands, or twitch responses in a given muscle group. Anderson [25] reported that 99 men who underwent myofascial release and progressive relaxation biofeedback experienced improvement, which was illustrated by a decrease in pain score, visual analog score, and urinary symptoms score. Patients were observed for a mean of 9.6 months. A prospective, randomized, controlled study to determine the long-term efficacy perhaps could transform this multidisciplinary approach to a mainstream therapy. However, one limitation to such treatment is the limited accessibility of subspecialized physical therapists and psychotherapists who perform this form of biofeedback and relaxation.

Conclusions

A consensus for the evaluation of patients with CP/CPPS was established in 2002. However, there are some limitations to the consensus because it does not include thorough psychosocial evaluation or examination or mapping of musculoskeletal disorders and myofascial trigger points. Monotherapies prescribed in an empiric fashion have less than optimal effects for our patients. Combining therapies empirically may seem attractive; however, inclusion criteria and evaluations may need to be expanded. One can ponder if treatment A affords 65% of patients a greater than 25% improvement and treatment B affords similar response; would the combination (A + B) lead to a greater number of patients improving or would the same proportion of patients experience a much greater degree of improvement?

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