Current treatment options in the management of chronic prostatitis

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Abstract: Chronic prostatitis is a disease with an unknown etiology that affects a large number of men. The optimal management for category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is unknown. The recent years have seen a significant increase in research efforts to understand, classify and treat CP/CPPS. Standard treatment usually consists of prolonged courses of antibiotics, even though well-designed clinical trials have failed to demonstrate their efficacy. Recent treatment strategies with some evidence of efficacy include: alpha-blockers, anti-inflammatory agents, hormonal manipulation, phytotherapy (quercetin, bee pollen), physiotherapy and chronic pain therapy. A stepwise, multimodal approach can be successful for the majority of patients who present with this difficult condition.

Keywords: prostatitis, chronic, treatment, management, CPPS

Introduction

Chronic prostatitis remains somewhat of an enigma in Urology. Ever since its description in 1968 (Meares and Stamey 1968) and initial attempt at classification 10 years later (Drach et al 1978), this condition has been long on hypotheses and short on hard data. The last 10 years have, however, seen significant growth in research on prostatitis, resulting in better evidenced-based therapies. This review will focus on the latest development on the treatment strategies developed for the treatment of category III/chronic pelvic pain syndrome (CPPS) of the NIH classification (Krieger, Nyberg, and Nickel 1999). Category III prostatitis (previously referred to as nonbacterial prostatitis or prostatodynia) is defined by the persistent symptoms of pelvic and genital pain and urinary symptoms without evidence for urinary tract infection.

General supportive measures

Although efficacy has not been demonstrated in clinical trials, men with CP/CPPS are frequently suggested to avoid spicy food, caffeine and alcohol, together with sitz baths. The issue of ejaculation is controversial, as some men report exacerbation of symptoms (Shoskes et al 2004) whereas other report reduction (Yavascaoglu et al 1999) with regular ejaculation. Stress has also been convincingly associated with CPPS. Indeed, in a well designed study, Ullrich et al (Ullrich et al 2005) reported greater perceived stress during the 6 months after the healthcare visit was associated with greater pain intensity and disability at 12 months. Based on those findings, stress reduction is frequently advocated. Importantly, stress reduction can assist in reducing the disability and response to pain. Furthermore, men with CP/CPPS are more likely to suffer from neurologic and psychiatric conditions then control patients (Pontari et al 2005).

Antimicrobials

At some point in the natural course of the disease, it is possible that bacterial infection is implicated in the etiology of CP/CPPS. Even though uropathogenic bacteria are

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cultured from a minority of patients with CP/CPPS, antimicrobial therapy is the most commonly prescribed treatment (McNaughton et al 2000). Importantly, there is no difference in culture results of urine and prostatic fluid between men with CPPS and asymptomatic controls.

The prostatic tissue is best penetrated by lipophillic drugs that have high pKa. In this group, we find the quinolones, the macrolides and sulfa drugs. Based on their pharmacokinetic profile, the quinolones are the drug of choice for patients with CP/CPPS. From a microbiological stand point, their broad spectrum (Chlamydia, mycoplasma and both gram positive and gram negative bacteria) also cover most uropathogens. In non-placebo controlled studies, ciprofloxacin, levaquin and lomefloxacin have all proved clinically effective for patients with category II prostatitis (chronic bacterial) (Naber, Busch, and Focht 2000; Naber and European Lomefloxacin Prostatitis Study Group, 2002; Wagenlehner et al 2005). Unfortunately, neither levaquin nor ciprofloxacin were found more effective than placebo in a randomized controlled trial in men with CPPS (Nickel et al 2003a; Alexander et al 2004). Macrolides such as azithromycin or clarithromycin also penetrate the prostate well (Giannopoulos et al 2001). These drugs have been reportedly used with some success in men with CP/CPPS (Skerk et al 2002, 2003, 2004), but never in the context of a randomized controlled trial. In light with the above-mentioned results, a critical analysis of the therapies for use in CP/CPPS, among which antibiotics, can be found in the Cochrane Database of Systematic Reviews, and the available data so far does not support use of antibiotics in CP/CPPS (McNaughton, Mac, and Wilt 2001).

The observed beneficial effect of antibiotics in some trials could be explained by a placebo effect or through a mechanism of action of the compounds not related to their antimicrobial activity. Antibiotics such as quinolones and macrolides have potent anti-inflammatory effects independent of their antimicrobial effects. It is also unclear if bacteria in the prostate proliferate in a environment protected by biofilms, as this may affect the choice of antibiotics (Arakawa et al 1999).

Despite these controversies, antimicrobials remain the most common treatment used in patients with CP/CPPS. While it appears that some patients with CP/CPPS show clinical improvement with antimicrobials, prolonged use without a documented infection or symptomatic improvement is unwarranted.

Prostate massage and ejaculation

Before the availability of broad-sprectum antimicrobials, prostatic massage was the mainstay of treatment for patients with prostatitis (O'Conor 1936). Mechanistically, prostate massage could help drain occluded prostatic duct and increase penetration of the gland by antimicrobial agents (Hennenfent and Feliciano 1998). It could also disrupt bacterial biofilms or massage a neuromuscular trigger point along the pelvic side wall. In a non-controlled study, prostate massage 2–3 times per week for 4–6 weeks with concurrent antibiotic treatment had some clinical benefit in patients with CP/CPPS (Nickel et al 1999). Frequent ejaculation achieves similar results (Yavascaoglu, Oktay, Simsek et al 1999). It has also been demonstrated that 40% of CP/CPPS patients treated with antibiotics and prostatic massage had lasting clinical improvement, especially if there was large volume of clumpy expressed prostatic secretions (EPS) at the first visit or if prostate cultures remained positive despite adequate antibiotics (Shoskes and Zeitlin 1999).

Alpha-blockers

CP/CPPS patients also frequently present with lower urinary tract symptoms (LUTS) of both obstructive and irritative nature. Furthermore, some of these patients will present with urodynamic evidence of bladder outlet obstruction (Barbalias, Meares Jr, and Sant 1983; Murnaghan and Millard 1984; Kaplan, Te, and Jacobs 1994; Mayo, Ross, and Krieger 1998; Liao, Shi, and Liang 1999). A subset of these patients will also have ultrasonographic evidence of bladder neck hypertrophy (Di Trapani et al 1988) with an accompanying obstructive pattern on uroflowmetry (Ghobish 2002). Such dysfunctional voiding is, however, probably not the predominant factor for the majority of men suffering from CP/CPPS (Murnaghan and Millard 1984; Mayo, Ross, and Krieger 1998) and the use of urodynamic testing in patients with CP/CPPS is not widely accepted (Strohmaier and Bichler 2000). Alpha-blockers can also have a direct effect on pain. It has been demonstrated that prostatic inflammation leads to substance P-mediated changes in the pain perception regions of the spinal cord and that these changes are blocked by tamsulosin (Ishigooka et al 2002). Importantly, the presence of urinary symptoms does not correlate with improvement in pain in CPPS patients who take alpha blockers.

A well designed study with alfuzosin was performed in patients with CP/CPPS and demonstrated a small, but statistically significant improvement in the NIH-CPSI score (Mehik et al 2003). The effect was only apparent after several months of treatment and disappeared when the treatment was stopped. Results with tamsulosin are mixed, with one study demonstrating a significant effect (Nickel et al 2004b) and an-

other one no effect (Alexander, Propert, Schaeffer et al 2004) when comparing against placebo. The latter negative study used a shorter treatment duration and included men who may have failed alpha blocker therapy in the past. Terazosin was also found to be superior to placebo in another study (Cheah et al 2004). Until larger definitive trials are completed, it appears reasonable to attempt treatment of CP/CPPS patients with 3–6 months of an alpha-blocker.

Anti-inflammatory

There is growing evidence that inflammation plays a significant role in CP/CPPS. Indeed, elevated levels of inflammatory cytokines (Alexander et al 1998; Miller et al 2002; Nadler et al 2000; Paulis et al 2003), low level of the anti-inflammatory cytokine interleukin-10 (Miller, Fischer, Goralnick et al 2002), reactive oxygen species (Pasqualotto et al 2000) and endorphin or prostaglandins (Shahed and Shoskes 2001) have all been associated with the diagnosis or symptom severity of patients with CP/CPPS when compared to healthy controls. It may be possible that an initial bacterial infection triggers a dysregulated inflammatory reaction.

Nonsteroidal anti-inflammatory drugs have long been used in CP. In a non-controlled study, it has been shown that ketoprofen suppository or oral nimesulide had some efficacy in CP/CPPS patients (Canale et al 1993). There is a well designed, blinded placebo-controlled study of an anti-inflammatory agent in CP/CPPS patients in which a small effect was observed (Nickel et al 2003b). Unfortunately, the drug used, rofecoxib, has been voluntary withdrawn by its manufacturer. Corticosteroids also have potent anti-inflammatory activity, and in a small, non-controlled study, prednisolone was effective in relieving symptoms of patients with CP/CPPS (Bates and Talbot 2000). One must carefully weigh the benefits and risk of using steroids to treat patients with CP/CPPS and their multiple side effects. Some phytotherapeutic agents, to be discussed later, may act by preventing inflammation.

Hormonal manipulation

The influence of androgen on the development of the prostate is well known, together with the effects of androgen deprivation. In a non-controlled study of men with CP/CPPS, finasteride use led to significant and durable improvement in symptoms (Kaplan, Volpe, and Te 2004). In a randomized, placebo controlled study of finasteride used in combination with other therapies, there was some symptom improvement seen (Nickel et al 2004a). The effect was small, however, and the authors did not recommend monotherapy with finasteride unless a significant component of BPH was present. Phytotherapeutic agents, to be discussed later, may act through similar mechanisms.

Surgery and minimally invasive therapy

Unless a specific indication is encountered during a work-up of patients with CP/CPPS, surgery does not have an important role in its treatment. In the 1980's, it was popular to try a "radical" TURP with mixed results (Barnes, Hadley, and O'Donoghue 1982) and it is no longer advocated for patients with CP/CPPS. With the introduction of minimally invasive therapy, a surgical option was again explored. Transurethral needle ablation (TUNA) of the prostate was shown to be of benefit in men with CP/CPPS in open-label studies (Lee et al 2002; Chiang and Chiang 2004). However, a sham controlled study could not demonstrate any efficacy of TUNA in men with CP/CPPS (Leskinen et al 2002a). Another minimally invasive approach is transurethral microwave therapy (TUMT). It has been studied in men with CP/CPPS, and found to be effective in non-controlled studies (Servadio and Leib 1991; Michielsen et al 1995; Mene et al 1997; Cho et al 2000; Leskinen et al 2002b; Kastner et al 2004). The main issue is whether the high temperatures used in BPH therapy are necessary for CP/CPPS and whether prostatic necrosis may lead to an increase in the inflammatory component of the condition. Sham controlled studies are required before these therapies can be recommended for routine use.

Alternative medicine

With an apparent dissatisfaction with 'standard' medical approach to the treatment of CP/CPPS, a large number of patients are seeking relief outside of traditional approaches. For instance, acupuncture has been reported to be effective in patients with CP/CPPS (Ge, Meng, and Xu 1988; Chen et al 1995; Chen and Nickel 2004;). However, none of those studies are adequately controlled.

Phytotherapy is another alternative to allopathic medications. Herbal-based therapies are prevalent and popular in urologic disease, more so in prostatic disorders, with compelling evidence (Shoskes 2002). Examples include: Chinese herbs (Jia et al 2001; Xu, Zhang, and Ding 2003; Han et al 2004;), green tea extracts (Lee et al 2005), quecertin (Shoskes et al 1999; Katske et al 2001), saw palmetto (Kaplan, Volpe, and Te 2004) and bee pollen (Buck, Rees, and Ebeling 1989; Buck et al 1990; Rugendorff et al 1993; Chen et al 2002; Elist 2006). Unfortunately, not all studies are adequately controlled.

Extracts of bee pollen are thought to be effective in prostatic conditions from their presumed anti-inflammatory and anti-androgen effects (Buck, Rees, and Ebeling 1989;

Buck, Cox, Rees, et al 1990). In an open-label study, 90 patients received one tablet of Cernilton N three times a day for 6 months. Excluding patients with complicating anatomic factors (urethral stricture, bladder neck stenosis or prostatic calculi) who had a minimal response to the treatment (1 or 18 patients saw improvement), 36% of the remaining patients were cured of their symptoms while another 42% saw their symptoms improved (Rugendorff, Weidner, Ebeling, et al 1993). In a double-blind randomized study with a different pollent extract (Prostat/Poltit), Elist et al reported significant clinical improvement when comparing with the placebo group (Elist 2006). Saw palmetto, probably the most commonly used phytochemical in prostatic conditions, is believed to act, in part, through an anti-androgen/anti-inflammatory mechanism has been tested in a open-label study in patients with CP/CPPS (Kaplan, Volpe, and Te 2004). However, it was not found to be more effective than placebo.

Quercetin, a polyphenolic bioflavonoid, is commonly found in red wine, green tea and onions (Hollman et al 1997; Hollman and Katan 1998). It is a biologically active compound with well demonstrated anti-inflammatory properties (Guardia et al 2001) and can, for instance, inhibit the production of inflammatory cytokines presumably implicated in the etiology of CP/CPPS such as tumor necrosis factor and interleukin-8 (Sato et al 1997). In a prospective, randomized double-blind placebo controlled study using the NIH-CPSI as end-point, 500 mg of Quercetin was administered twice a day for 4 weeks to CP/CPPS patients (Shoskes, Zeitlin, Shahed, et al 1999). Patients receiving quercetin had a significant improvement over the placebo group. Using prostaglandin E2 in expressed prostatic secretion as a surrogate marker of prostate inflammation, it was later found that quecertin significantly decreased inflammation in the prostate (Shahed and Shoskes 2000, 2001).

Neuromuscular and chronic pain therapy

Patients with CP/CPPS will often complain of pain and spasm of the pelvic floor muscles. Therapies aimed at relaxation of these muscle groups and proper use of pelvic floor muscle may therefore be expected to be beneficial. Unfortunately, not very many large clinical trials have been published, data is available from small trials. For instance, biofeedback physical therapy and pelvic floor re-education lead to a significant improvement of the NIH-CPSI score in men with CP/CPPS (Cornel et al 2005). In another study, myofascial trigger point release and pelvic floor re-education also lead to a significant improvement in NIH-CPSI score (Anderson et al 2005) and also improved sexual function in men with CP/CPPS (Anderson et al 2006). Also, a sham-controlled study of men with CP/CPPS found that electromagnetic therapy could significantly improve the NIH-CPSI score of the patients, with the greatest improvement in the pain related symptoms (Rowe et al 2005). Amytriptyline (Holroyd et al 2001) and gabapentin (Covington 1998) can both be useful for the management of chronic pain and chronic muscle pain conditions and we have used them with some success in the management of patients with CP/CPPS.

Prostatic stone therapy

The role of prostatic calcification is unclear in the etiology of CP/CPPS. Indeed, many asymptomatic older men have stones detected during transrectal ultrasound. However, large, central calcifications are often associated with symptoms in younger men (Geramoutsos et al 2004). Nanobacteria have attracted attention of late with their possible implication in biomineralization (Kajander et al 2001). With medical therapy against both nanobacteria and prostatic stones, it has been demonstrated that patients who had failed conventional therapy for CP/CPPS saw their NIH-CPSI significantly improve after such therapy (Shoskes, Thomas, and Gomez 2005). Such an approach awaits validation through a placebo-controlled study.

Treatment approach

Given current data, we favor a complete examination of the patient followed by multimodal therapy. In a treatment naive patient, a 2–4 week course of antibiotics is reasonable, but should not be continued if cultures are negative and there is no improvement in symptoms. If cultures are negative, we then use a combination of an alpha blocker (tamsulosin, alfusozin) and anti-inflammatory phytotherapy (quercetin and bee pollen, for instance 1 capsule of Q-Urol (Farr Labs, Santa Monica CA) twice daily) for 6–12 weeks. If not successful, we use neuromuscular therapies such as pelvic muscle physical therapy, amytriptiline or gabapentin. In patients who don't respond to conventional therapy and have prostatic stones on transrectal ultrasound, we use an anti-nanobacterial therapy such as Calciclear (Calgenex Corp, Tampa FL). In the minority of patients who do not improve with these therapies, referral to a pain management specialist is appropriate.

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