Review

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The Effect of α-Blockers Monotherapy vs. Combination Antibiotic Therapy on Symptom Alleviation in Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome

Kyu Shik Kim, Hong Sang Moon

Department of Urology, Hanyang University College of Medicine, Seoul, Korea

Prostatitis is a pathologic state of prostate inflammation accompanied by lower urinary tract symptoms and pelvic pain, reducing the quality of life in males of all ages. There is currently no established treatment modality for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). In this review, alpha-blocker monotherapy was compared with combination antibiotic therapies. Alpha-blockers are the most commonly used medications to treat CPPS, administered to over 40% of CPPS patients. The use of antibiotics in CP/CPPS is an alternative treatment option. There are no studies showing the efficacy of antibiotics in CP/CPPS patients. However, antibiotics are commonly prescribed to patients with CP/CPPS, often leading to patient improvement. A combined regimen of alpha-blocker, antibiotic, and anti-inflammatory therapy showed improvement in patient symptoms; however, the results were similar to monotherapy with alpha-blockers. When alpha-blocker monotherapy was compared with three multidrug therapies via randomized controlled trials, monotherapy was shown to be more effective than multidrug treatment. There is no definite treatment for CP/CPPS because it is caused by various factors, and symptoms are different for each patient. CP/CPPS patient care should be managed in a manner that identifies and treats all symptoms simultaneously and appropriately. Recently, urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness (UPOINT) was introduced in order to better treat patients. However, UPOINT has not been extensively studied in clinical trials, and the mechanical principles of UPOINT have yet to be elucidated. Alpha-blocker monotherapy and antibiotic combination therapy showed considerable improvement in CP/CPPS patients (by National Institutes of Health Chronic Prostatitis Symptom Index scores).

Keywords: Prostatitis; Anti-bacterial agents; Monotherapy

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Correspondence to: Hong Sang Moon
http://orcid.org/0000-0003-2101-1019
Department of Urology, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153 Gyeongchun-ro, Guri 11923, Korea
Tel: +82-31-560-2372, Fax: +82-31-560-2377
E-mail: moonuro@hanyang.ac.kr

INTRODUCTION

Prostatitis can manifest as an inflammatory state (acute or chronic), as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), or as asymptomatic prostatitis. Approximately 10% of acute prostatitis patients develop CP/CPPS, and 10% of them are diagnosed with CP/CPPS [1]. Over 95% of CP/CPPS patients are diagnosed with prostatitis in the absence of bacterial infection [2]. CP/CPPS describes a state without cancer, infection, or anatomical abnormality, but with urological pain or pelvic pain concurrent with voiding symptoms or sexual dysfunction. To be clinically diagnosed as CP/CPPS, symptoms must have been present for at least 3 of the last 6 months. Occasionally, cognitive impairment, sexual disorders, or emotional disorders are also present [3,4].

CP/CPPS reduces the quality of life via symptoms similar to angina pectoris in myocardial infarction [4]. The etiology of CP/CPPS has not well elucidated thus far, but inflammation, autoimmunity, neurological disorders, bladder and sphincter disorders, or mental health-related diseases have been all suspected [5]. In various studies, CP/CPPS has shown no correlation with inflammation. Despite repeatedly negative polymerase chain reaction test results, bacterial DNA has been detected in the prostate tissues of some CP/CPPS patients; in these patients, symptoms improved with antibiotic treatment [6,7]. It can therefore be presumed that, like *Helicobacter pylori* in gastrointestinal ulcer, bacteria that are difficult to grow using general culture techniques might exist in CP/CPPS patients. In another study, as a result of culturing urine and prostatic secretions from CP/CPPS patients using the Meares-Stamey localization technique, *Chlamydia trachomatis* and *Trichomonas vaginalis* were detected and found to contribute to inflammation [8]. Inflammation sometimes requires physical therapy, as it can cause neuromuscular dysfunction [9]. Sensitization of the central nervous system further causes depression, anxiety, and other neurological symptoms that might require antipsychotic medication [10].

Decades ago, CPPS was treated using antibiotics only after identifying the specific bacteria as the cause of the disease. To identify such a cause, cultures of urine and prostatic secretions were performed, and suitable antibiotic treatment implemented when appropriate. However, it has been reported that treatment with specific antibiotics was not effective for symptom improvement [11]. In the early 2000s, studies showed the effectiveness of various therapeutic methods and medications other than antibiotics for the treatment of CP/CPPS; these included randomized placebo- or sham-controlled trials [11].

Recently the urinary, psychosocial, organ-specific, infection, neurologic/systemic, and tenderness (UPOINT) phenotyping system, which concurrently detects various etiologies represented in patients and treats symptoms, was introduced. Nevertheless, there is no standard therapy for CP/CPPS. In this review, various monotherapies and complex therapies based on alpha-blockers and antibiotics were comparatively analyzed.

MONOTHERAPIES

To date, there has been a plethora of multidisciplinary studies on monotherapy with alpha-blockers, antibiotics, hormones, anti-inflammatory medicines, antispasmodics, and non-medication therapies. However, most of these studies have failed to provide promising therapeutic strategies for CP/CPPS patients. However, a few alpha-blocker monotherapies have shown positive, promising results. A prospective longitudinal study by the National Institutes of Health (NIH) Chronic Prostatitis Collaborative Research Network of men with CP/CPPS found that more than 40% of study participants had received previous treatment with alpha-blockers [12].

1. Alpha-Blockers

Generally, alpha-blockers are used to treat lower urinary tract symptoms. They relax the smooth muscles of the prostate and urinary tract, extending the bladder volume. In addition, they suppress pain and improve neurogenic inflammatory reactions. They are significantly effective in improving CP. In a previous study using a rat model, alfuzosin reduced neurogenic inflammatory reactions [13]. In transient receptor potential vanilloid 1-expressing sensory neurons, it reduced the inflammatory reaction by inhibiting substance P. It also showed that inflammation decreased with a reduction in C-fos-immunoreactive cells [13]. The mechanism of pain improvement conferred by alpha-blockers remains unknown. There is one hypothesis, which suggests that pain is reduced as alpha-blockers control the reflex arcs of the spinal cord [14]. Various randomized

controlled trials using alpha-blockers to treat CP have shown positive results.

1) Alfuzosin

When administering alfuzosin to 66 CP/CPPS patients for 6 months, remarkable improvement in pain was observed, based on the NIH Chronic Prostatitis Symptom Index (CPSI). Even after discontinuation of medication, persistent pain was absent [15]. Similarly, in a study using alfuzosin for 12 weeks in 272 patients, pain improvement of at least 4 points using the NIH-CPSI was observed. Depression, quality of life, and anxiety were similar between the patient group and control group [16]. In a separate CP/CPPS study comparing an alfuzosin-treated group with a small control group (n=40) for 6 months, remarkable NIH-CPSI improvements were observed [15]. Thus, at least a 12-week treatment period should be considered to when opting to use alfuzosin. Currently, there are no clear therapeutic guidelines available for second-generation selective alpha-blockers. Further research is needed.

2) Silodosin

Silodosin is a third-generation alpha-blocker, and its advantage has been shown in studies on CP/CPPS. In randomized clinical trials targeting 151 patients, silodosin was administered to those showing pain for at least 3 months. As a result of administering 4 mg/d or 8 mg/d for 12 weeks, significant improvements were observed with respect to the NIH-CPSI scores (after a washout period of 4 weeks) compared with the placebo-administered control group. Patients receiving 8 mg/d saw bigger improvements than those receiving 4 mg/d. Global Response Assessment scores also showed significant improvements with the 4 mg/d dose [17].

3) Tamsulosin

Tamsulosin is a third-generation alpha-blocker, and several studies have focused on this drug as a monotherapy for CPPS. A 2-week study targeting 58 patients with pelvic pain for at least 3 months was performed. In this short-term study, patients were advised to take 0.4 mg tamsulosin. With a 2-week washout, its usefulness was confirmed on the 15th and 45th day after intake (compared with the control group). A decrease of at least 6 NIH-CPSI points was considered patient improvement. By the 45th day, 25% showed remarkable improvement (i.e., improvement of very severe symptoms), and over 50% showed improvement. It is worth noting that, on the 15th day, there were no significant improvements, with respect to the NIH-CPSI score, voiding symptoms, or quality of life [18]. In a separate study targeting 100 patients with pelvic pain or discomfort for at least 3 months, 0.2 mg tamsulosin was administered for 6 months. Pain reduction status was measured using NIH-CPSI, and patients were followed up for 2 years. After 3 and 6 months, the NIH-CPSI scores in treated patients showed significant improvements over those in the control group. For a group in which administration was discontinued after 6 months, recurrence of symptoms was seen by the 12th or 24th month, and medication for these symptoms was required [19].

4) Doxazosin

In clinical research using doxazosin (a second-generation alpha-blocker) to treat CP/CPPS, positive results were reported [20]. In CP/CPPS patients receiving only doxazosin or a combination of doxazosin and anti-inflammatory drugs for 6 months, pain improvement after discontinuing the medication was maintained for 6 months [20]. In addition, the quality of life improved for both groups and maintained throughout the research period. There was no significant difference in improvement between the two groups [20].

5) Terazosin

Positive results have also been observed with terazosin, which is another second-generation alpha-blocker. After the administration of terazosin to CP/CPPS patients for 14 weeks, NIH-CPSI total scores were remarkably decreased [21]. Pain, voiding symptoms, and quality of life were all improved 14 weeks after treatment. Compared with the control group, these improvements were significant ($p<0.001$). However, no difference between the treatment and control groups was observed 6 months after the treatment [22].

2. Antibiotics

Antibiotics are a first-line treatment for acute prostatitis, but efficacy of their use in CP/CPPS is not clearly supported by research. Some studies have reported that ciprofloxacin, levofloxacin, azithromycin, doxycycline, and clarithromycin reduce inflammation and improve other symptoms. However, in many of these prospective, placebo-controlled studies,

guidelines for antibiotic selection were inconsistent since the same antibiotic yielded various results. The long-term improvement rate in CP/CPPS patients using antibiotics is 50-60% [23]. Failure in CP/CPPS treatment is often attributed to the combined use of various drugs and antibiotics [24]. Antibiotic use in CP/CPPS is a selective and empirical treatment. In a study using ciprofloxacin (500 mg per day) [25] or levofloxacin (500 mg 4 times per day) [26] for 6 weeks, NIH-CPSI symptom improvement in the control group was evident, but without statistical significance. This was likely due to the small number of study participants. Zhou et al. [27], who made a comparison between tetracycline (500 mg 2 times per day) and placebo for 12 weeks, showed that the NIH-CPSI score was reduced by 18.5 points in the treatment group, with statistical significance. In CP/CPPS testing negative in bacterial culture tests, studies showing the need for antibiotics are lacking. Nevertheless, antibiotics are commonly prescribed to CP/CPPS patients, and some studies have reported symptom improvement [28,29]. A recent meta-analysis of antibiotic treatments for CP/CPPS revealed overall symptom improvements, but these improvements were not always statistically significant [30]. Thus, despite the randomized clinical trials using antibiotic monotherapy for CP/CPPS, specific guidelines for treatment have not yet been clarified.

COMBINATION THERAPIES

1. Combinations of Alpha-Blockers and Antibiotics

Alexander et al. [31] performed a 6-week study in CP/CPPS patients, comparing 0.4 mg tamsulosin, 500 mg ciprofloxacin (twice per day), tamsulosin+ciprofloxacin, and placebo. The results were measured by NIH-CPSI, and all treated groups showed improvement. There was no statistically significant difference between the groups, and combination therapy (tamsulosin and ciprofloxacin) was not better than monotherapy. Similar results have been reported in other studies using antibiotics and alpha-blockers. In a prospective, randomized trial to compare monotherapy and combination therapy (levofloxacin and doxazosin) for 6 weeks, monotherapy showed better improvement than combination therapy, according to NIH-CPSI [32]. In another study, NIH-CPSI scores were compared after administering monotherapy (tamsulosin) or combination therapy (tamsulosin and diclofenac or tamsulosin and ciprofloxacin) for 8 weeks. In that research, all 3 groups showed NIH-CPSI improvements, although the biggest improvement was observed in the tamsulosin monotherapy group. There was no statistically significant difference between the three groups [20]. In a separate study, monotherapy (alpha-blockers) or combination therapy (alpha-blockers, anti-inflammatory drugs, and muscle relaxants) was administered to CP/CPPS patients for 6 months. The average baseline NIH-CPSI score was 23.1 in the monotherapy group and 21.9 in the combination therapy group. After 6 months, the NIH-CPSI average score was 10.7 in the monotherapy group and 9.2 in the combination therapy group, without statistically significant difference between the two groups. Based on this result, alpha-blocker monotherapy might be preferred to antibiotic combination therapies in terms of effectiveness and stability [33].

In one study, conflicting result was reported. Patients received monotherapy using levofloxacin, terazosin, and combination of both. After 6 weeks, the NIH-CPSI scores were improved in each group. There was an improvement of 45.1% in the levofloxacin group (n=38); 22.4% in the terazosin group (n=38); and 50.0% in the combination therapy group (n=38). Thus, among the three groups, the combination therapy group showed the biggest improvement. However, there was no statistically significant difference between the groups [34]. In general, research performed thus far has shown that monotherapies with antibiotics or alpha-blockers produce excellent effects. While combining antibiotics with alpha-blockers could be clinically relevant for certain patients, research in this area is lacking. It is clear that further studies are required.

Each monotherapy has its advantages and disadvantages, as evidenced through research. At times, therapies not clinically available (such as the use of phytotherapeutic agents) have also been attempted. The reason that a defined therapy has not been established, despite the extensive research, is that CP/CPPS is a syndrome that involves various factors. Symptoms manifest differently depending on the patient. As such, it is hard to treat CP/CPPS patients with monotherapy on a long-term basis. It has been suggested that CP/CPPS could be better treated after clarifying the diagnosis. UPOINT was recently introduced. Its ability to recognize 6 domains of clinical expression in patients has helped physicians approach treatment in a diversified way.

The 6 clinical domains are urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic findings, and tenderness of muscles. UPOINT was named according to the first letter in each of these domains [25]. Evaluation is performed using NIH-CPSI scores in each area. The NIH-CPSI system uses a total score that reflects the sum of each domain score. UPOINT guides physicians in administering multimodal therapy that is matched with patient symptoms. However, many studies have not included UPOINT, and treatment algorithms have not always been clarified. Studies that evaluate each UPOINT domain and between domains are needed. Because long-term evaluations of UPOINT are lacking, verification of its efficacy over time will also be necessary [25]. Time and economic losses in finding the appropriate treatment method based on patient symptoms are considerable. When any therapy for a certain symptom does not work well, continued treatment must involve re-evaluation. It is hoped that the use of UPOINT will minimize these losses and improve patient outcomes.

Alpha-blocker therapy is commonly used to treat CP/CPPS. Its efficacy has been verified by numerous randomized clinical trials. For patients who do not require a complex diagnostic process, who cannot complete the diagnostic process, or who cannot afford extensive care, monotherapy with alpha-blockers is the recommended therapy.

CONCLUSIONS

Based on most studies to date, although the mechanisms of improvement conferred by alpha-blockers has not been clearly verified, both alpha-blocker monotherapy and antibiotic combination therapy showed considerable improvement in CP/CPPS patients (by NIH-CPSI scores).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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