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The Effect of α-Adrenergic Antagonists in Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Meta-Analysis of Randomized Controlled Trials

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Abstract

The effectiveness of α-adrenergic antagonists on patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) has not been supported by well-evaluated study. The meta-analysis was performed to supply the best evidence about use of this class of drugs in CP/CPPS. A fully recursive literature search to June 2005 was conducted in PubMed, EMBASE, the Cochrane Controlled Trials Register, and the Chinese Biomedicine Database to identify potentially relevant randomized controlled trials. RevMan4.2 was used for statistical analysis. Nine studies with 734 patients were included. Combined analysis showed a significant reduction of total NIH-CPSI or I-PSS in patients with treatment duration of more than 3 months. There were also valuable results in urinary symptom alleviation. Alphα-adrenergic antagonists did not show benefit in pain. The meta-analysis revealed that the use of α-adrenergic antagonists was warranted in CP/CPPS, and the treatment duration should be long enough (more than 3 months).

Key words: Evidence-based medicine, prostate, drug treatment

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is common in adult males. The prevalence ranges from 2%–10%, and 15% of men experience symptoms during their lifetimes (Krieger 2004), including genitourinary and pelvic pain, dysuria, obstructed urinary stream, nocturia, and frequency of urination. It makes a great impact on quality of life and increases economic expenditure (Turner et al, 2004). The diagnosis is mainly based on the syndrome, and no objective measurement exists so far (McNaughton Collins et al, 2000). On the other hand, the etiology of CP/CPPS is ambiguous; bacteria infection has been proved not to be the cause of the symptoms, and inflammatory or abnormal activity of pelvic nerve and muscle may play a role (Schaeffer, 2004). Such men are classified as having National Institutes of Health (NIH) category III prostatitis, which is the most common of the clinically defined prostatitis syndromes (Hua and Schaeffer, 2004).

CP/CPPS is also refractory and puzzles urologists. Because the cause is unknown at present, various empirical treatments are adopted in clinical practice, such as α-adrenergic antagonists, antibiotics, nonsteroidal anti-inflammatory agents, finasteride, hyperthermia, and surgery (Pontari, 2003; El-Hakim, 2004). Nevertheless, none of them are supported by credible evidence. Therefore, evidence-based management is essential for both clinicians and patients. We evaluated all the acquirable studies to try to supply the best evidence for the treatment of CP/CPPS.

Materials and Methods

Search Strategy

The following databases were searched for relevant articles published in English or Chinese to June 2005: PubMed (from January 1980), EMBASE (from January 1989), Cochrane Controlled Trials Register, and Chinese Biomedicine Database (from 1980). The key words were the following Medical Subject Heading (MeSH) terms and/or text words: adrenergic alpha-antagonists, prostatitis, chronic prostatitis, pelvic pain, and chronic pelvic pain syndrome. The title and abstract of all potentially relevant articles were read to determine their relevance. Full articles were also scrutinized if the title and abstract were unclear.

Inclusion Criteria

The following are the criteria for the included studies. First, they should be open or blind randomized studies. Second, patients should be diagnosed with chronic prostatitis or chronic pelvic pain syndrome (CP/CPPS), category III. Chronic or acute bacterial prostatitis, acute urinary retention, urethral stricture, benign enlargement, bacteriuria, prior prostate surgery, and cancer were excluded. Third, patients randomly received α-adrenergic antagonists and placebo. The details of treatment methods should be described and raw data was available in included studies.

Assessment of Methodological Quality

The assessment of methodological quality was undertaken by 2 of the authors independently, and differences in assessment were solved by consensus. From each study, data were extracted on the type of patients, the method of treatment, and the effectiveness of treatment.

Jadad score and allocation concealment were adopted to evaluate the methodological quality of each trial (Moher et al, 1996): 0 for nonrandomized controlled trials, 1–2 for poor-quality trials, and 3–5 for high-quality trials. The concealment of allocation also was divided into 3 grades: A for adequate concealment, B for unclear concealment, C for inadequate concealment.

Statistical Methods

RevMan 4.2 software supplied by Cochrane Collaboration (Oxford, United Kingdom) was used. The effect size of categorical variables was odds ratio (OR) and 95% confidence intervals (CI) calculated from the raw data of the selected studies. For numerical variables, if the unit was identical, weighed mean difference (WMD) was used, and standardized mean difference (SMD) was used when the unit was different. The homogeneity of adopted trials was tested before meta-analysis. If the heterogeneity had no statistical significant difference, a fixed-effects model was used during meta-analysis. Otherwise, a random-effects model or subgroup analysis was adopted.

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Study Characteristics

Eighty-five papers were obtained by searching the databases. No more articles were identified by manual search. All trials were identified for further evaluation after the title and abstracts were read. Nine measured up to the criteria and were included (Gul et al, 2001; Evliyaoglu and Burgut, 2002; Wang et al, 2002; Cheah et al, 2003; Mehik et al, 2003; Alexander et al, 2004; Lu et al, 2004; Nickel et al, 2004; Shen et al, 2004). Sixty-four were excluded because they were animal studies, review articles, or irrelevant to the current study. There were no repetitive studies or meta-analysis. The Table shows the characteristics of included studies.

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Characteristics of included studies

The Effects of α-Adrenergic Antagonists

Nine studies compared the value of α-adrenergic antagonists in treatment of CP/CPPS with placebo; a total of 734 patients were randomly assigned to receiving one kind of α-adrenergic antagonists or placebo. All studies were finished in the past 8 years. They were conducted in the United States (Alexander et al, 2004), Canada (Nickel et al, 2004), Turkey (Gul et al, 2001; Evliyaoglu and Burgut, 2002), Finland (Mehik et al, 2003), Malaysia (Cheah et al, 2003), and China (Wang et al, 2002; Lu et al, 2004; Shen et al, 2004), respectively. Five studies are high-quality (Jadad score $\geq$ 3); none of them adopted intention-to-treat analysis. Criteria for including or excluding in each study design were clear. The allocation concealment in 1 study is adequate, but not mentioned in the others. The duration of α-adrenergic antagonist treatment varied from 4 weeks to 6 months. NIH-CPSI or I-PSS scores were adapted to evaluate the severity of symptoms. Six articles supplied the NIH-CPSI or I-PSS scores before and after treatment. Two supply the change of score before and after treatment. Three did not supply the raw data in text, but the figures in 2 articles can be measured for raw data. One study was excluded in meta-analysis for failure to get the data (as shown in Figure 1 and Figure 2).

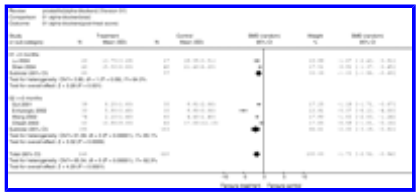

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Figure 1. Effect of α-adrenergic antagonists on total score.

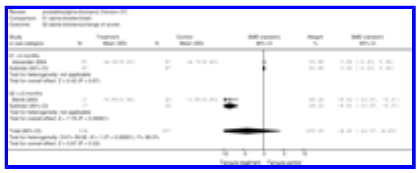

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Figure 2. Effect of α-adrenergic antagonists on total score.

Figure 1 shows the outcome of meta-analysis of 6 studies, comparing the posttreatment scores. A total of 466 patients were included. In 2 studies including 117 patients for whom treatment durations of less than 3 months were reported, the combined SMD was −1.23 (95% CI = −1.96 to −0.49). The other 4 studies including 349 patients compared the effectiveness of α-adrenergic antagonists after being managed for more than 3 months; the combined SMD was −2.00 (95% CI = −3.19 to −0.82). Meta-analysis of all 6 studies showed that the combined SMD was −1.73, favoring treatment (95% CI = −2.52 to −0.94), but heterogeneity existed.

Figure 2 shows the outcome of 2 studies comparing the change of score before and after treatment. A total of 211 patients were included. There was heterogeneity, so SMD was adopted. The combined SMD was −4.16 (95% CI = −12.57 to 4.25).

Effect of α-Adrenergic Antagonists on Pain

Four studies compared the effect of α-adrenergic antagonists on pain in patients with CP/CPPS. Meta-analysis of 3 studies including 183 cases showed that the combined SMD was −2.44 (95% CI = −4.93 to 0.05) (Figure 3).

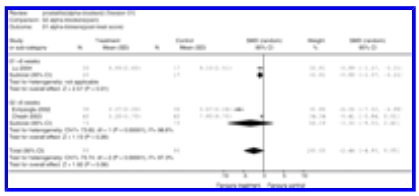

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Figure 3. Effect of α-adrenergic antagonists on pain.

Effect of α-Adrenergic Antagonists on Urinary Symptoms

Meta-analysis of 2 studies including total 123 cases showed the effect of α-adrenergic antagonists

on urinary symptoms of CP/CPPS. The combined SMD was −1.60 (95% CI = −2.24 to −0.96) (Figure 4).

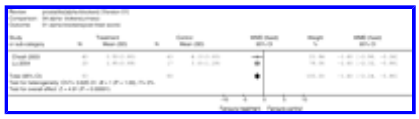

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Figure 4. Effect of α-adrenergic antagonists on urinary symptoms.

Effect of α-Adrenergic Antagonists on Quality of Life

Three studies compared the effect of α-adrenergic antagonists on quality of life. Meta-analysis of 2 studies showed that the combined WMD was −1.40 (95% CI = −1.47 to −1.33) (Figure 5).

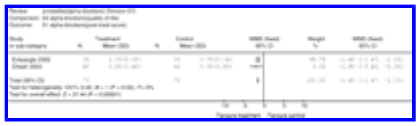

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Figure 5. Effect of α-adrenergic antagonists on quality of life.

Discussion

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CP/CPPS is a complex problem for both urologists and patients for its high morbidity and refractory. It is difficult to explain the etiology, pathology, and symptoms of CP/CPPS by 1 simple mechanism. Approximately half of all men may experience the symptoms of CP/CPPS through their lifetime, which could have an impact on sexual function or prostate cancer (Dennis et al, 2002). Various kinds of methods have emerged in trying to cure CP/CPPS or alleviate the symptoms, but all of them are based on a small sample size or uncontrolled studies of experiences. Recently, many studies designed strictly have been reported about the effectiveness of treatment used in practice for patients with CP/CPPS, including some multicenter, randomized, controlled studies. However, the results were controversial. The reason for conflicting conclusions is attributed to diverse factors, such as type of medicine, accompanying treatment, treatment duration, etc. A sufficiently large number of cases can control these biases to a receptible extent. The aim of meta-analysis is to evaluate and combine the eligible small-case studies quantitatively by strict statistical methods and determine the best estimate of treatment effect. Therefore, meta-analysis is thought to be able to provide the best evidence for decision-making.

For this meta-analysis, a specific research question was defined, a comprehensive literature search was conducted, and explicit criteria for study selection and methodological quality assessment were used. In the overall analysis, it was revealed that long-term use of α-adrenergic receptor blockers (more than 3 months) had an effect on improvement of symptoms in patients with CP/CPPS, mainly in voiding symptoms. However, the conclusions from overall analysis were weakened by the degree of heterogeneity of the results.

Subgroup analyses were performed in an attempt to explain the heterogeneity present and understand which subgroups might benefit the most. The most prominent limitation in this meta-analysis was the different approaches used in the raw data supplements, that is, mean score and change of score. The results of studies had to be processed respectively according to the raw data supplement when analyzing, rather than conducting an overall analysis. Therefore, the value of conclusions was influenced. Figure 1 shows the α-blockers can reduce the total score. Nevertheless, one study, the Chronic Prostatitis Collaborative Research Network conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a high-quality, multicenter, randomized, placebo-controlled trial, did not show any benefit of α-blockers in terms of total NIH-CPSI, pain score, urinary score, or quality-of-life score. It is should be noted that treatment duration of α-blockers in this study conducted by NIDDK was only 6 weeks. Therefore, the treatment duration may be one important factor to achieve satisfactory effectiveness. It is suggested that management with α-blockers in CP/CPPS should continue for not less than 3 months.

NIH-CPSI can be employed to evaluate the severity of CP/CPPS symptoms quantitatively, and some authors have adopted I-PPS to evaluate them. They are both excellent choices for evaluating the effectiveness of treatment. NIH-CPSI evaluates the symptoms of CP/CPPS in 3 aspects, pain, urinary symptoms, and quality-of-life; hence, the analysis is also conducted on the 3 aspects respectively (Krieger et al, 1999). But I-PSS was designed for evaluation of benign prostatic hypertrophy; it does not include the measurement of pain. A study conducted by Evliyaoglu designed a pain questionnaire as well. Meta-analysis suggests that there is no significant improvement in pain compared to placebo by treatment of α-adrenergic antagonists. The study conducted by NIDDK shares the same conclusion. This may be attributed to the fact that the pain of CP/CPSS was not only caused by the abnormal of smooth muscle tone within the prostate gland and prostatic capsule and in the region of the bladder neck. Various factors play a role in the mechanism of pain in CP/CPPS, such as inflammation and other neuromuscular diseases. Further evaluation is needed in this conclusion, because the other articles did not supply the details of NIH-CPSI results.

Alphα-adrenergic receptor blockers such as tamsulosin and terazosin have been proved effective in treating voiding symptoms attributed to benign prostatic hypertrophy (McConnell et al, 2003). These drugs are used empirically in patients with CP/CPPS because such patients have similar voiding symptoms. The analysis showed that α-blockers may be helpful to the improvement of urinary symptoms in patients with CP/CPPS. The conclusion supported the empirical use of α-blockers in CP/CPPS in practice. Although the data from the NIDDK study do not support such results, the treatment duration in the NIDDK study was only 6 weeks, so a longer treatment with α-blockers may be warranted in CP/CPPS. The pharmacologic effect of selective α-blockers is to relax the smooth muscle tone within the prostate gland and prostatic capsule and in the region of the bladder neck in patients with benign prostatic hyperplasia, which leads to the alleviation of obstructive and irritative voiding symptoms of the lower urinary tract in men with benign prostatic hyperplasia; it may also reduce voiding pressures and improve voiding flow dynamics in men with CP/CPPS (Lowe, 2004). The mechanism of α-blockers in the treatment of CP/CPPS may be that they can relax the neck of the urinary bladder and prostatic urethra, prevent the reflux of urine, and improve the stability of the detrusor muscle.

According to the meta-analysis, α-adrenergic antagonists are warranted in treatment in patients with CP/CPPS. Longer duration of treatment with α-adrenergic antagonists may be beneficial. Alleviation of the tension generated by edema of noninfectious inflammation through relaxation of smooth muscles of the stroma may be speculated to contribute to the subjective response of the prostatitis to α-adrenergic receptor blockers monotherapy. However, a number of factors are involved in the

mechanisms of the symptoms of CP/CPPS; therefore, more treatment strategies proved by meta-analysis based on high-quality, randomized, controlled trials are essential for CP/CPPS.

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