Infections

A Placebo-Controlled Comparison of the Efficiency of Triple- and Monotherapy in Category III B Chronic Pelvic Pain Syndrome (CPPS)

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Abstract

Objectives: To perform a prospective, placebo-controlled study to examine the efficacy of α-blocker compared with triple therapy (α-blocker, anti-inflammatory, and muscle relaxant) in the treatment of Category IIIB chronic pelvic pain syndrome (Category IIIB CPPS).

Materials and methods: The study was conducted between September 2004 and December 2005, and included 90 treatment naïve patients, aged 22–42 yr (mean age: 29.1 ± 5.2) with Category IIIB CPPS, who were randomized into three groups: group 1, α-blocker; group 2, combination of α-blocker, anti-inflammatory, and muscle relaxant; group 3, placebo once daily. The patients were treated for 6 mo and were followed up for a further 6 mo. Changes from baseline in the total and domain scores of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) were evaluated. The primary criterion for response was scoring ≤2 on the NIH-CPSI quality of life item. The secondary criterion for response was >50% reduction in NIH-CPSI pain score.

Results: The NIH-CPSI initial and sixth-month total scores were 23.1 and 10.7, respectively, in group 1, and 21.9 and 9.2, respectively, in group 2. The initial and sixth-month scores remained stable in group 3 (22.9 and 21.9, respectively). There was no statistically significant difference between two treatment arms with respect to efficiency of treatment (p > 0.05). The responses in groups 1 and 2 were found durable at the end of 12 mo.

Conclusions: We found that α-blocker monotherapy was as effective and safe as triple therapy in the treatment of Category IIIB CPPS.

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1. Introduction

Chronic prostatitis is an important health care problem because it is the most common urologic diagnosis for men younger than 50 yr and the third most common diagnosis after benign prostatic hyperplasia (BPH) and prostate cancer for men older than 50 yr [1]. Chronic prostatitis decreases quality of life [2] and could lead to resource consumption and economic losses because those affected have a high rate of absenteeism from and low-production at work [3]. The National Institutes of Health (NIH) Prostatitis Collaborative Network developed a new classification system and symptom score because conservative diagnosis and classification systems were inadequate [4]. Assessments are made in three main categories (pain, voiding, and quality of life) in symptom scoring. According to this classification, the most common form is Category III, which is subdivided into Category IIIA and Category IIIB depending on the presence or absence of inflammatory cells in the prostatic fluid.

The treatment of men with chronic pelvic pain syndrome (CPPS) is difficult because the pathogenesis is unclear. Several treatment modalities such as antimicrobial drugs, muscle relaxants, α-blockers, and biofeedback physical therapy as a monotherapy or combination therapy have been proposed and investigated [5].

This study compares α-blocker with triple therapy (α-blocker, anti-inflammatory, and muscle relaxant) and placebo for treatment of noninflammatory CPPS (Category IIIB).

2. Materials and methods

This prospective randomised study was performed in three centres (Bakirkoy Teaching Hospital, Taksim Teaching Hospital, Vakif Gureba Teaching Hospital) between September 2004 and December 2005. Patients who were classified as having Category IIIB chronic prostatitis were included in this study. The diagnosis of Category IIIB CPPS included a detailed history and physical examination, transrectal ultrasound, urine flow measurement, residual urine volume measurement, and standard microbiologic cultures and microscopic analysis of urine (before and after prostatic massage) and prostatic secretions (if available).

2.1. Inclusion and exclusion criteria

Eligibility requirements included patients with

- a diagnosis of Category IIIB CPPS, aged 20–45 yr;
- a score of ≥ 1 on items 1 and 2 (pain and discomfort);
- a score of ≥ 4 on item 9 (quality of life) of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI);
- symptoms for ≥ 3 mo;
- a desire to be treated.

Potential subjects were excluded from the study under the following conditions:

- Those who met the criteria for chronic bacterial prostatitis or Category IIIA CPPS after lower urinary tract localisation studies [6].
- Those who had had previous urinary tract infection or a uropathogen documented within the last year.
- Those who had significant medical problems.
- Those who had any NIH consensus exclusion criteria [4].
- Those who had been treated or were taking medications that could affect lower urinary tract function.

Ninety patients (aged 22–42 yr; mean age: 29.1 ± 5.2) were randomised into three groups in order of appearance: group 1, α-blocker (doxazosin 4 mg/d); group 2, combination of α-blocker (doxazosin 4 mg/d), anti-inflammatory (ibuprofen 400 mg/d), and muscle relaxant (tiocolchicoside 12 mg/d); group 3, placebo with patients receiving one placebo tablet per day. Placebo tablets compounded of lactose had a similar appearance to doxazosin tablets. Ibuprofen was given at a low dose, with an effort to avoid side-effects during the long period of treatment. Patients were prospectively treated for 6 mo and then followed up for an additional 6 mo. Patients were assessed by NIH-CPSI at the beginning and at the end of the therapy and at the end of the sixth month after the therapy was finished. The Turkish version of the NIH-CPSI, which is currently in the process of validation, was used in this study. The primary analysis was the mean change in CPSI between the three groups from baseline (pretreatment) at the end of the sixth month. Secondary analyses included (1) the change in CPSI from baseline (pretreatment) at the end of the 12th month, (2) the changes in subscores at the end of 6 and 12 mo, and (3) the responder subanalyses at the end of 6 and 12 mo. The primary criterion for response was scoring ≤ 2 (“delighted-to-mostly satisfied”) on the NIH-CPSI quality of life item. The secondary criterion for response was > 50% reduction in NIH-CPSI pain score. Other outcomes included peak urinary flow rate and postvoid residual between treatment groups. In addition, during each follow-up visit, subjects were asked if they experienced any adverse effects.

A weight transducer flowmeter was used to measure peak urinary flow with values considered evaluable only if the voided volume was at least 150 ml. Transabdominal ultrasound was used to measure postvoid residual urine. Pillai trace test for multiple comparisons and Bonferroni test for dual comparisons were used in the statistical analysis of the data.

3. Results

Eighty-three of the initial 90 patients were eligible for evaluation after 6 mo, and 79 patients were
eligible at the end of 12 mo. In group 1, 12 (40%) patients and, in group 2, 17 (56%) patients experienced side-effects compared with 7 (23%) patients in the placebo group. Side-effects in groups 1, 2, and 3 included dizziness (3 and 4 vs. 2 patients, respectively), postural hypotension (3 and 4 vs. 1, respectively), gastrointestinal complaints (2 and 6 vs. 2, respectively), palpitation (1 and 2 vs. 1, respectively), flulike syndrome (2 and 1 vs. 0, respectively), and headache (1 and 0 vs. 1, respectively). Seven patients were finally excluded from group 3 because of gastrointestinal complaints. In the sixth month after completion of the therapy, one patient each in groups 1 and 2, and 2 patients in group 3 dropped out. The patients who dropped out were included in the secondary responder subanalyses as nonresponders.

The NIH-CPSI total score in group 1 dropped to 10.7 in the sixth month compared with an initial score of 23.1, and was found to be 12.5 at the end of 12 mo. In group 2, these scores were 9.2 in the sixth month compared with an initial score of 21.9, and were found to be 11.7 at the end of 12 mo. The NIH-CPSI scores of the patients in group 3 remained stable, that is, 21.9 in the sixth month and 22.2 at the end of 12 mo, compared with the initial 22.9.

Using the primary criterion, we obtained the following response rates: 63% (19 of 30 patients), 63% (19 of 30 patients), and 33% (10 of 30 patients) for groups 1, 2, and 3, respectively. Using the secondary criterion, we obtained response rates of 66% (20 of 30 patients), 70% (21 of 30 patients), and 33% (10 of 30 patients) for groups 1, 2, and 3, respectively. For the primary criterion, durable responses occurred in 40% (12 of 30 patients) of group 1, 40% (12 of 30 patients) of group 2, and 20% (6 of 30 patients) of group 3. For the secondary criterion, durable responses occurred in 43% (13 of 30 patients) of group 1, 43% (13 of 30 patients) of group 2, and 20% (6 of 30 patients) of group 3. Group 1 and group 2 had similar reductions in the NIH-CPSI total score and individual domain scores that were greater than group 3 ($p < 0.001$; Table 1). There was no statistically significant difference between the two groups with respect to efficiency of treatment ($p > 0.05$). Of note was the statistically significant change in quality of life impact in groups 1 and 2 compared with the placebo group, which was consistent until the end of the 12th month. There was no difference in peak urinary flow rate or postvoid residual between the various groups. Parameters that were not associated with response included age, baseline urinary and quality of life impact domains, NIH total score, peak urinary flow rate, postvoid residual, and symptom duration.

4. Discussion

The management of CPPS is controversial, mainly because of the unclear pathogenesis of this disease. There are many proposed mechanisms for the development of symptoms, and the suggested methods of treatment address these mechanisms.

Patients with Category IIIB CPPS have significantly more lower urinary tract symptoms, which appear to be related to poor relaxation of the bladder neck during voiding [7,8]. The subsequent turbulent “dysfunctional” voiding may predispose the patient

| Table 1 – Changes in NIH-CPSI scores, Qmax, and PVR values in all three groups of patients |
|-----------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Group 1                                 | NIH-CPSI total score (items 1–9) | NIH-CPSI pain score (items 1–4)  | NIH-CPSI Urinary (items 5 and 6) | NIH-CPSI quality of life impact (items 7–9) | Qmax (ml/s)a | PVR (ml) |
| Initial                                 | 23.1 (1.8)                       | 9.9 (1.6)                         | 5.2 (1.0)                         | 8.0 (0.9)                         | 15.9 (5.3)   | 22.3 (6.7) |
| 6 mo                                    | 10.7 (1.3)b                      | 4.7 (1.2)b                        | 2.2 (0.8)b                        | 3.8 (1.1)b                        | 16.7 (5.9)   | 20.6 (6.1) |
| 12 mo                                   | 12.5 (1.0)b                      | 5.1 (0.8)b                        | 2.9 (0.6)b                        | 4.5 (0.8)b                        | 16.2 (5.6)   | 21.0 (6.2) |
| Group 2                                 | Initial                          | 21.9 (1.5)                        | 8.8 (1.4)                         | 6.9 (1.4)                         | 6.2 (0.9)    | 16.2 (5.4) |
| 6 mo                                    | 9.2 (1.0)b                       | 3.4 (0.7)b                        | 3.4 (0.8)b                        | 2.4 (0.9)b                        | 16.7 (5.5)   | 22.7 (6.5) |
| 12 mo                                   | 11.7 (1.3)b                      | 5.1 (0.9)b                        | 4.0 (0.9)b                        | 2.6 (1.1)b                        | 16.6 (5.5)   | 22.8 (6.5) |
| Group 3                                 | Initial                          | 22.9 (1.2)                        | 9.2 (0.9)                         | 6.6 (0.8)                         | 7.1 (1.1)    | 17.2 (6.4) |
| 6 mo                                    | 21.9 (1.2)                       | 8.5 (0.8)                         | 6.4 (1.0)                         | 6.9 (1.1)                         | 17.5 (6.6)   | 22.7 (6.9) |
| 12 mo                                   | 22.2 (1.1)                       | 8.7 (0.9)                         | 6.5 (0.9)                         | 7.0 (1.0)                         | 17.1 (6.4)   | 22.6 (6.5) |

NIH-CPSI = National Institutes of Health Chronic Prostatitis Symptom Index; PVR = postvoid residual; Qmax = maximum urinary flow rate.

a Voided volume of at least 150 ml.

b Statistically significant difference compared with placebo.
to reflux of urine into the prostatic ducts, causing intraprostatic inflammation and subsequently pain [9]. The bladder neck and prostate are rich in α-receptors, and it is hypothesised that α-blockade may improve outflow obstruction, improving urinary flow, and perhaps diminishing intraprostatic ductal reflux [10]. α-Blockade, which is used successfully to treat lower urinary tract symptoms associated with BPH, may ameliorate Category IIIB CPPS symptoms by improving urinary voiding parameters.

Several studies have investigated the effect of α-blocker therapy in patients with CPPS and showed a significant improvement in NIH-CPSI total score compared with placebo [11–15], mostly during a long-term follow-up of up to 6 mo [14,16]. Our results support these findings with regard to durability of response after the cessation of treatment with an α-blocker.

Conflicting results have been reported with the use of tamsulosin. Alexander et al. [17] reported that tamsulosin did not substantially reduce symptoms compared with placebo in men with long-standing Category IIIB CPPS, who had at least moderate symptoms [17]. However, they added that patients who had received less pretreatment might have responded differently. Our patients responded both to monotherapy with an α-blocker and to triple therapy. This difference may be due to two reasons: First we included only those patients who were not previously treated, and second the treatment period of 6 mo was longer than the 6 wk reported in the Alexander et al. study.

On the contrary, the study of Nickel et al. [18], in which 58 patients were randomised to 0.4 mg tamsulosin or to placebo, showed that tamsulosin provided symptomatic relief of moderate and severe Category IIIB CPPS. Furthermore, the efficacy of tamsulosin was dependent on the baseline for the total and for the pain and urinary symptom domains of the NIH-CPSI, and increased as the baseline score increased. We observed significant improvement in the doxazosin group. The changes of NIH-CPSI between baseline scores and those at the end of 6 mo of treatment were statistically significant (p < 0.001). The ratios of response in both treatment arms were still higher than the placebo group 6 mo after the cessation of treatment (40% vs. 20%).

Nonsteroidal anti-inflammatory drugs theoretically should improve the inflammatory parameters due to chronic prostatitis and possibly result in a reduction of symptoms. Dinis et al.’s [19] study on human cadavers found the existence of rich capsaicin receptors or transient receptor potential subfamily vanilloid type 1 receptor sensory innervation in the human prostate [19], which suggests that new therapeutic perspectives may be required for the treatment of pain in patients with chronic prostatitis (CPPS). Canale et al. [20] found that nimesulide quickly reduced inflammatory-type symptoms such as dysuria, strangury, and painful ejaculation [20]. However Nickel et al. [21], who compared a cyclooxygenase-2 inhibitor, rofecoxib, with placebo, showed that the placebo caused an unexpectedly significant and durable response. They suggested that, because the placebo response appeared to level off at the end of 6 wk, a longer study might demonstrate a larger treatment effect. Because our study was designed to treat patients for 6 mo and a significant response to placebo was not anticipated, treating patients with a low dose of ibuprofen (i.e., 400 mg/d) seemed reasonable. It is our opinion that this might have decreased the incidence of side-effects, which may be expected during a relatively long period of treatment.

Different combination therapies have been tried including α-blockers in combination with antibiotics, muscle relaxants in combination with analgesics, antibiotics, and so forth; although patients showed improvement, the results were associated with side effects [11,17]. The kind of triple therapy presented in our study has never really been compared with monotherapy and placebo in a prospective way. Anecdotal use of combination therapy (high dose α-blocker, narcotic analgesic, and muscle relaxant) has been reported. Although patients showed improvement, the disadvantages were impairment of quality of life and need for hospitalisation [5]. Shoskes et al. [22] assessed 53 patients with a diagnosis of Category IIIB CPPS who received multimodal therapy, antibiotics, prostatic massage, anti-inflammatory phytotherapy, α-blockers, and neuromuscular agents. He concluded that step-wise therapy with various agents could be successful in the majority of patients with long-standing chronic prostatitis. However, this study was not a prospective and placebo-controlled study.

Many investigators feel that CPPS is the ultimate reflection of a smooth and skeletal neuromuscular dysregulatory phenomenon in the perineum or pelvic floor [11,23]. In one of the few studies that compared muscle relaxants with placebo, Osborn et al. [11] conducted a prospective double-blind study comparing phenoxybenzamine, baclofen, and placebo in 27 prostatodynia patients. Patients were treated with each agent for 1 mo in a crossover trial. Symptomatic improvement was seen in 37% of the patients treated with baclofen compared with 8% of those treated with placebo. Addition of the muscle relaxant thiocolchicoside in our study did not add a significant advantage to monotherapy with
α-blocker. Cornel et al. [24] demonstrated a significant effect of biofeedback physical therapy and pelvic floor reeducation for Category IIIB CPPS patients. The correlation between the pelvic muscle tonus results with NIH-CPSI score is highly suggestive of the fact that the pelvic floor plays an important role in the pathophysiology of Category IIIB CPPS. These findings may indicate the existence of a multifactorial genesis of CPPS and may explain the different results observed in some studies.

In this prospective, randomised study, we found that when an α-blocker–only group and a combination group were compared with a placebo group, there was a significant decrease in NIH-CPSI total score and pain score according to initial scores. However, triple therapy provided no advantage over α-blocker therapy. A significant and durable success rate was achieved in the α-blocker group and in the combination therapy group, probably because of adequate duration of treatment and the fact that the patients were treatment naïve.

5. Conclusions

We found that α-blocker monotherapy was as effective and safe as triple therapy in the treatment of treatment-naïve patients with Category IIIB CPPS. In addition, it was more economical and tolerable than triple therapy. Both therapies are significantly more effective than placebo.

References

Editorial Comment
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Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), also defined as National Institutes of Health (NIH) III prostatitis, is the most common urologic diagnosis in men under the age of 50 and its impact on quality of life is similar to that of myocardial infarction or Chron’s disease [1]. The diagnosis is based on the presence of chronic pelvic pain and lower urinary tract symptoms; depending on presence or absence of inflammatory cells in the semen or prostatic fluid, CP/CPPS is classified into NIH IIIA and NIH IIIB prostatitis, respectively.

The presence of inflammatory cells would suggest NIH IIIA CP/CPPS to be an infectious disease whereby the responsible microbiologic agent has been eliminated (or is not identified with common microbiologic tests [2]). As a matter of fact, irritative urinary voiding symptoms are prevalent in such patients. Conversely, the absence of inflammatory cells and the prevalence of obstructive urinary symptoms in patients with NIH IIIB CP/CPPS questions the role of infection in such clinical conditions and would rather speak for poor relaxation of the bladder neck during voiding.

The present randomised, controlled trial showed that both monotherapy with α-blockers and triple therapy with α-blockers and anti-inflammatory and muscle relaxant agents provided, in comparison with placebo, a significant and durable reduction in NIH-Chronic Prostatitis Symptom Index scores in patients with NIH IIIB CP/CPPS. Such positive results were probably due to adequate treatment duration (6 mo) and study population (well-selected treatment-naïve patients). The study also showed that monotherapy with α-blockers was as effective as triple therapy, thus suggesting that blockade of α1-receptors in the bladder neck is what is really needed to relieve symptoms.

It is, however, interesting to note that, as already shown by Cheah et al. [3], α-blockers improved the urinary symptoms without improving the relatively bad peak urinary flow (mean Q_{max}, 16 ml/s) of these young patients (mean age, 29 yr) with NIH IIIB CP/CPPS, thus suggesting the presence of a structural rather than a functional obstruction.

Further support for the hypothesis of structural obstruction is provided by recent transrectal ultrasound findings of “posterior prostate lip” in patients with CP/CPPS [4].

Taking these findings together, there are grounds to assume that NIH IIIB CP/CPPS could be a sort of bladder-neck contracture. We do not know whether such contracture is primary or secondary to chronic prostatic inflammation evolving into bladder-neck fibrosis, but we know that α-blockers provide significant symptomatic relief for at least 6 mo in well-selected treatment-naïve patients, as shown by the present study and that of Cheah et al. [3], moderate and short-lasting symptomatic relief in patients with recurrent disease [5,6], and no symptomatic relief in patients with long-lasting heavily retreated disease [7]. In these last patients bladder-neck incision provides significant and long-lasting improvement of both symptoms and urinary flow.

References