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# Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA)

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## Abstract

We investigated the effectiveness of celecoxib in reducing symptoms in patients with difficult chronic pelvic pain syndrome (CPPS), NIH category IIIA. Sixty-four patients with category IIIA CPPS were randomized into two groups of 32 subjects each. One group was treated with celecoxib (200 mg daily) and the other with placebo. All patients underwent treatment for 6 weeks and were evaluated clinically before (baseline) and after 1, 2, 4, 6, and 8 weeks of treatment. The evaluation included the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) and a subjective global assessment (SGA). Repeated measures analysis of variance was used to evaluate treatment and time effects and their interaction. A decrease (means ± SD) in total NIH-CPSI score from 23.91 ± 5.27 to 15.88 ± 2.51 in the celecoxib group and from 24.25 ± 5.09 to 19.50 ± 2.50 in the placebo group was observed during treatment (0 to 6 weeks). A statistically significant decrease was observed in pain subscore ($P < 0.006$), quality of life subscore ($P < 0.032$) and total NIH-CPSI score ($P < 0.015$) after 2, 4 and 6 weeks, but not in urinary subscore. In addition, 38% of the celecoxib and 13% of the placebo subjects had at least a moderate improvement in SGA. The trend was similar for the NIH-CPSI scores. However, the response to treatment in terms of total NIH-CPSI score or subscore was not significantly different from placebo after interruption of treatment for 2 weeks. Our results show that celecoxib provides significant symptomatic improvement limited to the duration of the therapy in patients with difficult category IIIA CPPS compared to placebo.

Key words: Prostatitis; Chronic pelvic pain syndrome; Cyclooxygenase inhibitors

## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common syndrome of unclear etiology with a significant impact on quality of life (1). CP/CPPS is classified into inflammatory [National Institutes of Health (NIH) IIIA] and non-inflammatory CPPS (NIH IIIB). In category IIIA, leukocytes can be found in expressed prostatic secretion (EPS), in the urine after prostatic massage, and in semen. In NIH IIIB no leukocytes are detectable (2).

There are no confirmed standard therapies for the treatment of CP/CPPS. Traditionally, therapies for CP/CPPS include antibiotics, α-blockers, phytotherapy, and other medical agents (3-7). However, part of the patients have refractory symptoms despite multiple treatment approaches (8).

Patients with CPPS have higher levels of tumor necrosis factor-α (TNF-α) and of the inflammatory cytokine interleukin-1β (IL-1β) in EPS and semen compared to normal men (9). This cytokine could up-regulate the level of cyclooxygenase-2 (COX-2) gene expression, which may further contribute to the development of inflammation (10). Celecoxib is a highly selective COX-2 inhibitor that inhibits primarily this isoform of cyclooxygenase by inhibiting prostaglandin production, whereas traditional non-steroidal antiinflammatory drugs (NSAIDs) inhibit both COX-1 and COX-2.

Celecoxib has been licensed for use in osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation, and menstrual symptoms, and to reduce the number of colon and rectal polyps in patients with familial adenomatous polyposis (11). According to known mechanisms, celecoxib

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and other COX-2 inhibitors would be expected to reduce inflammation and pain while minimizing gastrointestinal adverse drug reactions (e.g., stomach ulcers) that are common with non-selective NSAIDs. Therefore, a pilot study was conducted to compare the efficacy of celecoxib to placebo for the treatment of patients with difficult category IIIA CPPS.

## Material and Methods

Patients were recruited between August 2006 and January 2008 for a double-blind randomized controlled trial, i.e., all patients aged 18-58 years with a clinical diagnosis of CP/CPPS (category IIIA) according to NIH consensus criteria were enrolled in the study. The CP/CPPS of patients had to be refractory (patient unsatisfied with their clinical response) to standard conventional therapy (antibiotics, α-blockers). Eligibility requirements included age between 18 and 58 years; symptoms of CP/CPPS for >6 months; ≥1 month of treatment with appropriate antibiotics or/and α-blockers; negative infection screening, including the four-glass test and bacterial localization studies; total National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score of 14 or more; NIH-CPSI pain score of 8 or more at baseline. Exclusion criteria were presence of chronic bacterial prostatitis after a 4-glass lower urinary tract localization test; previous urinary tract infection or a uropathogen documented within the last year; cancer of the genitourinary tract; a history of active genital herpes within the previous year; active urethral stricture; inflammatory bowel disease; a history of pelvic radiation or systemic chemotherapy; a history of intravesical chemotherapy; prostate or bladder surgery, and neurologic disease affecting the bladder. All patients underwent a physical examination and standardized history, a 4-glass lower urinary tract localization test, semen evaluation (microscopy and culture), and a urethral swab (culture).

The study was a 8-week, double-blind, randomized, placebo-controlled investigation with a 2-week placebo run-in. After the placebo run-in the patients were randomized to receive celecoxib 200 mg/day or identical looking placebo tablets. Randomization was performed by a computer software program (Microsoft Excel, version 7.0, Random Number Generation analysis tool). All patients underwent the treatment for 6 weeks. The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, and written informed consent was obtained from all patients.

At the beginning of the study, the 64 patients were evaluated by the same urologist using a standardized history, physical examination, and symptom score evaluation with the NIH-CPSI questionnaire to identify the three main aspects of this disorder, i.e., pain, urinary dysfunction and quality of life. After the 1st, 2nd, 4th, and 6th weeks of therapy, all patients underwent another physical examination and filled out the NIH-CPSI questionnaire again. In addition, a subjective global assessment (SGA) (12-15) was completed during the 1st, 2nd, 4th and 6th weeks after the baseline assessment.

To distinguish treatment responders from non-responders, patients with more than a 25% decrease in their total NIH-CPSI score were defined as responders. Moreover, the degree of subjective improvement was assessed at the 1st, 2nd, 4th, and 6th weeks compared to baseline values using the SGA. With SGA the patient's improvement was graded as none (≤25% improvement), mild (25-50% improvement), moderate (50-75% improvement), or marked improvement (>75%). Responders were pre-defined as those who indicated that they had a moderate or marked improvement in their global symptoms.

Differences between and within the two treatment groups over time were assessed using repeated-measures analysis of variance. This analysis allowed us to test for a main effect of treatment (celecoxib *vs* placebo), time effect and time by treatment interaction. The time effect alone would imply that the treatment itself had no specific effect on the variable of interest. A treatment-by-time interaction would imply that subjects responded to a specific treatment over time with a significant response. *Post hoc* analyses were done using independent sample *t*-tests with 2-tailed significance. Results were considered to be significant when $P \leq 0.05$. All tests were 2-tailed.

The responder analysis data were treated descriptively. All statistical analyses were performed using the SPSS statistical software packages (SPSS for Windows 16.0; SPSS Inc.; USA).

## Results

Celecoxib and placebo were generally well tolerated. All 64 patients completed the study. Of 3 patients who reported adverse clinical experiences, 2 in the celecoxib group had mild diarrhea and a skin rash and 1 in the placebo group had nausea. However, the adverse experience did not prevent the patient from completing the study.

The treatment effect (difference between treatment groups in the change from baseline) is shown in Figure 1. Repeated-measures analysis of variance revealed a significant group-by-time interaction for pain subscore ($P < 0.001$), urinary subscore ($P < 0.01$), quality of life subscore ($P < 0.001$) and total NIH-CPSI score ($P < 0.001$) in the celecoxib group compared with the placebo group. *Post hoc* analyses showed that celecoxib significantly reduced the pain subscore ($P < 0.006$), quality of life subscore ($P < 0.032$) and the total NIH-CPSI score ($P < 0.015$), compared to placebo after 2, 4, and 6 weeks. However, treatment had no significant effect on urinary subscore. We also investigated the duration of symptoms after the interruption of treatment. No significant difference was detected regarding the total NIH-CPSI score and subscore between the celecoxib group and placebo group after treatment discontinuation (8 weeks). Our results

showed that celecoxib ameliorates symptoms in men with difficult category IIIA CPPS with an action limited to the duration of the therapy or perhaps slightly longer, but without a durable effect sustained over time.

Table 1 describes the percentage of responders in each treatment group. At 6 weeks, a significantly greater percentage of patients in the celecoxib group demonstrated a 25% decrease in total NIH-CPSI score compared to the placebo group (78 *vs* 31%, for a ≥25% total NIH-CPSI decrease). Similarly, SGA analysis demonstrated improvement in the celecoxib group compared to the placebo group (56 *vs* 41%, with a ≥25% improvement and 38 *vs* 13%, with a ≥50% improvement).

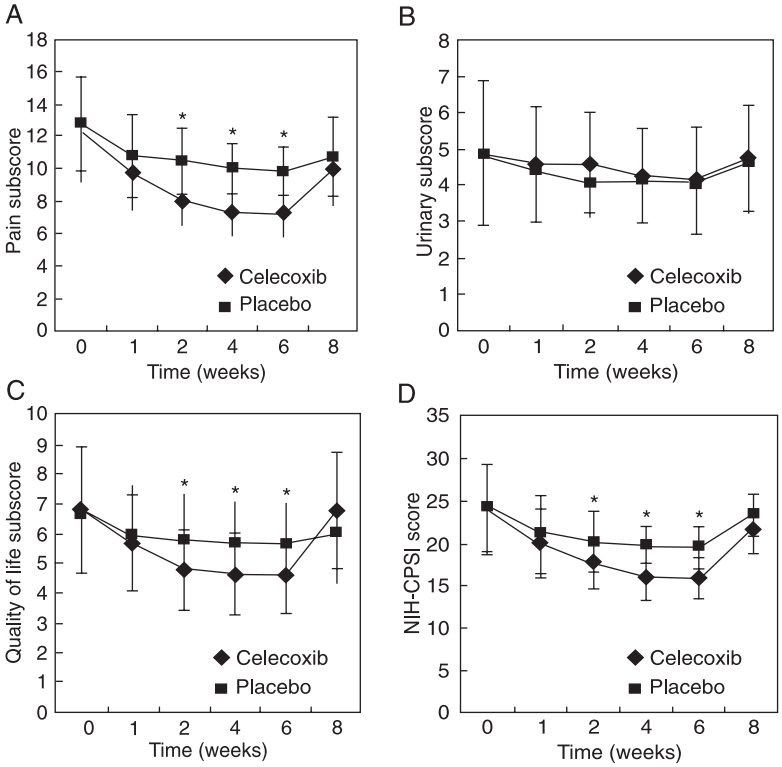


**Figure 1.** Time plots of the effectiveness of celecoxib and placebo on patients with difficult chronic prostatitis/chronic pelvic pain syndrome. Data are reported as means ± SD. *A*, *C*, and *D*, Significantly reduced pain subscore, quality of life subscore and total NIH-CPSI score after 2, 4 and 6 weeks. However, there was no significant effect of treatment on urinary subscore (B). NIH = National Institutes of Health; CPSI = Chronic Prostatitis Symptom Index. *P < 0.05 compared to celecoxib treatment (independent samples *t*-test).

## Discussion

The etiology of CP/CPPS is still unknown, with a consequent difficulty in management of the disease. Traditional medical therapy is often unsuccessful and fails to improve the symptoms of most patients with CPPS (3). Thus far, there are no formal guidelines for the management of CP/CPPS.

The role of abnormal proinflammatory cytokines in CP/CPPS has been recently studied (16,17). Cytokines are soluble signaling molecules produced by leukocytes as well as endothelial, epithelial and other cell types. They act locally over short cellular distances as initiators and modulators of immune and inflammatory responses. Increased concentrations of TNF-α and IL-1β have been reported in seminal plasma and EPS in CPPS (9,16). These cytokines could up-regulate COX-2 gene expression levels, which may further contribute to the development of inflammation (10). These findings raised the possibility of a role of proinflammatory cytokines in the pathogenesis of CPPS and of the COX-2 inhibitor in the relief CPPS symptoms.

A previous pilot study suggested that rofecoxib treatment may be of benefit to men diagnosed with CPPS (13), with high-dose rofecoxib (50 mg) providing a statistically significant but only a modest clinical

**Table 1.** Responders to celecoxib therapy *vs* placebo among patients with difficult chronic prostatitis/chronic pelvic pain syndrome.

| Variable | Celecoxib | | | | | Placebo | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 week | 2 weeks | 4 weeks | 6 weeks | 8 weeks* | 1 week | 2 weeks | 4 weeks | 6 weeks | 8 weeks* |
| NIH-CPSI decrease | | | | | | | | | | |
| ≥25% | 22% | 81% | 84% | 78% | 31% | 16% | 25% | 34% | 31% | 19% |
| SGA improvement | | | | | | | | | | |
| ≥25% | 42% | 75% | 66% | 56% | 28% | 31% | 31% | 38% | 41% | 22% |
| ≥50% | 3% | 9% | 22% | 38% | 13% | 0% | 3% | 13% | 13% | 6% |

Data are reported as percent of responders. Patients (N = 32/group) were treated with 200 mg/day celecoxib or placebo for 6 weeks. NIH = National Institutes of Health; CPSI = Chronic Prostatitis Symptom Index; SGA = subjective global assessment. *Two weeks after interruption of the 6-week treatment.

benefit compared to placebo. Zeng et al. (18) evaluated the efficacy and safety of celecoxib in treating type IIIA CP/CPPS, and obtained mean NIH-CPSI total scores that were significantly different from placebo. Moreover, the dosage of 200 mg twice a day is more effective than that of 200 mg daily. However, to date, no clinical studies have focused on the use of a COX-2 inhibitor for the treatment of difficult CP/CPPS. Therefore, we evaluated the efficacy of celecoxib, a drug that lowers COX-2 levels in the prostate, in the treatment of patients with difficult CP/CPPS.

The NIH-CPSI, a validated symptom index, is used in men with symptoms suggestive of CP/CPPS to quantify symptoms and response to treatment. The questionnaire has proved to have a high degree of internal consistency and reliability when self-administered in clinical practice by patients with CP/CPPS.

Using the scores obtained from the NIH-CPSI questionnaires, we compared the efficacy of celecoxib to that of placebo in patients with difficult CP/CPPS. We observed a significant amelioration of chronic prostatitis-related symptoms during the treatment period. Improvement in pain subscore, quality of life subscore and total NIH-CPSI score did reach significance over placebo after 6 weeks of therapy, but no significant decrease in urinary subscore was observed. In addition, a greater proportion of patients on celecoxib experienced a 25% decrease in total NIH-CPSI score compared to placebo. At the end of therapy (6 weeks), 13% of the placebo group had a ≥50% decrease in SGA compared to 38% of the celecoxib group.

CP/CPPS is a clinical syndrome characterized by pain in the perineum, pelvis, suprapubic area or the external genitalia, with variable degrees of voiding disturbance. Alpha-blockers have been proposed for the treatment of CP/CPPS since a voiding dysfunctional explanation for this syndrome was hypothesized in the early 1980's (19). The theory has been recently confirmed by other reports (20). In our study, we found that improvement in urinary subscore did not reach significant levels over placebo after 6 weeks of therapy. This result might suggest that the COX-2 inhibitor celecoxib reduces pain symptoms.

We conclude that therapy with celecoxib is well tolerated and provides a significant improvement in men with difficult CP/CPPS. However, conclusions reached in a study on such a small sample clinical trial must be interpreted with caution. A trial with a larger sample size may provide more definitive information about the efficacy and safety of celecoxib.

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