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Clinical Significance of National Institutes of Health Classification in Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Purpose: We determined the effects of alpha-blockers and quinolone in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) classified by National Institute of Health (NIH) consensus group.

Materials and Methods: Data from a total of 111 patients who were diagnosed with CP/CPPS between June 2010 and June 2012 were analyzed retrospectively. The patients were classified into group 1 (category IIIA, n=40) and group 2 (category IIIB, n=71). Treatment using alfuzosin and levofloxacin was given to both groups for 6 weeks. International Prostate Symptom Score (IPSS) and NIH Chronic Prostatitis Symptom Index were measured before and after therapy.

Results: Group 1 had a significant decrease in total IPSS score, CPSI pain score, CPSI quality of life (QoL) score, and total CPSI score (p=0.043, p=0.006, p=0.015, and p=0.006, respectively). Group 2 had a significant decrease in IPSS voiding symptom score, IPSS storage symptom score, total IPSS, CPSI pain score, CPSI voiding score, CPSI QoL score, and total CPSI score (p=0.002, p=0.004, p=0.001, p=0.001, p=0.006, p=0.001, and p=0.001, respectively). The CPSI score was reduced by 6 points or more in 50.0% of patients (n=18) in group 1 and in 51.6% of patients (n=32) in group 2. However, there was no statistically significant difference between the changes in IPSS and CPSI scores across the 2 groups.

Conclusions: Although combination treatment reduced the CPSI score in both groups, there was no significant difference between the groups after combination treatment. We suggest that factors other than inflammation also contribute to symptoms associated with CP/CPPS.

Keywords: *Adrenergic alpha-antagonist; Anti-bacterial agents; Leukocytes; Prostatitis*

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INTRODUCTION

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) represents one of the most commonly encountered disease entities. About 25% of patients who come to a urology clinic are thought to belong to the chronic prostatitis group [1].

Currently, the National Institutes of Health (NIH) classifies prostatitis into 4 categories depending on urine and prostatic fluid analysis, which includes microscopic examination and cultures. Of all cases, more than 90% of symptomatic prostatitis is categorized as NIH category type III, which is defined by the presence of chronic pelvic pain and possibly voiding symptoms without uropathogenic bacteria. The new NIH classification for category III further defined these men as either category IIIA (inflammatory) or IIIB (noninflammatory) on the basis of the presence of significant white blood cells (WBCs) in prostatic-specific specimens (i.e., expressed prostatic secretion [EPS], urine specimen after prostatic massage [VB3], and semen) [2,3], However, although some research has confirmed the effectiveness of various treatments according to the NIH classification, no difference in outcome was shown in the two groups. Therefore, this study was conducted to evaluate clinical outcomes in the treatment of CP/CPPS according

to NIH classification.

MATERIALS AND METHODS

A retrospective review was performed of 111 patients with a diagnosis of CP/CPPS who were managed at Yonsei University Wonju Severance Christian Hospital between June 2010 and June 2012. The diagnosis of CP/CPPS was made by physical examination, microscopic analysis of urine and standard microbiological cultures, transrectal ultrasonography, and serum prostate-specific antigen (PSA) measurements. Patients were included in the study if they had experienced pain or discomfort in the pelvic region for at least 3 months [4]. We excluded patients with urinary tract infection, hypoechoic lesions on transrectal prostate ultrasound, serum PSA levels greater than or equal to 4 ng/dL, a history of antibiotic treatment in the 6 months preceding the initial visit, invasive prostate-related procedures (transurethral resection of the prostate, transurethral incision of the prostate, or transurethral needle ablation), genitourinary cancer, inflammatory bowel disease, active urethral stricture, prostate or bladder surgery, or neurologic diseases affecting the bladder.

Depending on the number of WBCs in the EPS or VB3, each patient was designated into the 2 NIH subgroups discussed above. A patient was assigned to the NIH category IIIA group if the WBC count in the EPS was equal to or greater than 10 per high power field (HPF) or the WBC count in the VB3 was equal to or greater than 5 per HPF. Conversely, a patient was assigned to IIIB if the WBC count in the EPS was less than 10 per HPF or the WBC count in the VB3 was less than 5 per HPF [2]. Both groups were evaluated before the treatment and 6 weeks after the treatment by using NIH Chronic Prostatitis Symptom Index (NIH-CPSI) scores and the International Prostate Symptom Score (IPSS). Determination of the presence or absence of the therapeutic effect was defined as when the CPSI score fell 6 points or more [5]. All the patients were treated with once-daily alpha-blockers (alfuzosin 10 g) and quinolone (levofloxacin 500 mg) for 6 weeks.

PASW ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The Wilcoxon signed-rank test was used to compare the baseline scores with posttreatment scores. Paired t-test and chi-square test were used to analyze the efficacy of treatment between groups. Treatment outcome was analyzed by logistic regression, adjusted for age, prostate volume, IPSS, and category of CP/CPPS. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the 111 patients, 41 were classified into group 1 (category IIIA) and 71 patients into group 2 (category IIIB) on the basis of WBCs and culture results. The patients' mean age was 54.91±11.75 years in group 1 and 51.15±13.43 years in group 2. The total IPSS was 12.87±9.87 for group 1 and 15.04±7.96 for group 2. The total CPSI was 20.29±7.72 in group 1 and 20.48±9.66 in group 2. Baseline characteristics including age, prostate volume, PSA, mean maximal urine flow rate on uroflowmetry, CPSI score, and IPSS were not significantly different between the two groups (Table 1).

Table 2 lists the mean IPSS and NIH-CPSI before and after the combination therapy. The total IPSS was significantly decreased in group 1 (from 16.00±10.86 to 12.14±9.02, p=0.043) and group 2 (from 17.93±5.19 to 17.00±7.32, p=0.001). The IPSS voiding symptom subscore was significantly decreased in group 2 (from 9.93±3.14 to 10.79±5.14, p=0.002). The IPSS storage symptom subscore was significantly decreased in group 2 (from 8.14±3.99 to 6.21±3.57, p=0.004). The CPSI pain score was significantly decreased in group 1 (from 8.28±4.68 to 5.33±3.64, p=0.006) and group 2 (from 8.52±5.13 to 5.94±4.32, p=0.001). The CPSI voiding symptom score was significantly decreased in Group 2 (from 5.00±3.35 to 3.65±2.72, p=0.006). The CPSI QoL symptom score was significantly decreased in group 1 (from 7.33±2.35 to 6.06±2.07, p=0.015) and group 2 (from 7.71±2.74 to 5.81±2.75, p=0.001). The total CPSI score was significantly decreased in group 1 (from 20.11±7.63 to 15.11±6.93, p=0.006) and group 2 (from 21.23±9.38 to 15.39±7.87, p=0.001). The CPSI total score was reduced by 6 points or more in 50% of the patients in group 1 (n=18) and 51.6% of the patients in group 2 (n=32). No significant differences (p=0.913) in treatment outcomes were observed between the two groups. As shown in Table 3, there were no statistically significant differences in treatment outcomes after adjustment for age, prostate volume, and IPSS.

TABLE 1. Baseline characteristics of patients with CP/CPPS

Characteristic	Prostatitis classification		
	IIIA (n=40)	IIIB (n=71)	p-value[a]
Age (y)	54.91±11.75	51.15±13.43	0.196
Prostate volume (mL)	29.04±13.28	28.79±10.14	0.925
PSA (ng/mL)	1.45±1.21	1.13±1.16	0.247
Qmax (mL/s)	16.33±9.73	15.85±7.20	0.182
CPSI			
Pain	9.00±4.78	8.43±5.44	0.686
Voiding	4.37±3.25	4.57±3.15	0.813
QoL	7.05±2.46	7.48±2.90	0.561
Total	20.37±8.05	20.65±9.64	0.909
IPSS			
Voiding	7.29±6.61	8.51±4.47	0.422
Storage	5.58±4.15	6.57±4.36	0.361
Total	12.87±9.87	15.04±7.96	0.321

Values are presented as mean±standard deviation.
CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; PSA, prostate-specific antigen; CPSI, Chronic Prostatitis Symptom Index; QoL, quality of life; IPSS, International Prostate Symptom Score.
[a]:Independent t-test.

TABLE 2. IPSS and CPSI among 2 groups before and after the α-blocker and quinolone treatment

	IIIA (n=40)			IIIB (n=71)		
	Pretreatment	Posttreatment	Difference	Pretreatment	Posttreatment	Difference
IPSS						
Voiding symptom	8.57±6.52	7.14±4.88	−1.43±2.63	9.93±3.14	10.79±5.14	−2.57±4.83[a]
Storage symptom	7.43±4.86	5.00±4.39	−2.43±3.10	8.14±3.99	6.21±3.57	−2.64±2.76[a]
Total	16.00±10.86	12.14±9.02	−3.86±4.10[a]	17.93±5.19	17.00±7.32	−5.43±5.18[a]
CPSI						
Pain	8.28±4.68	5.33±3.64	−2.94±4.08[a]	8.52±5.13	5.94±4.32	−2.58±3.88[a]
Voiding symptom	4.56±3.14	3.72±3.19	−0.83±1.68	5.00±3.35	3.65±2.72	−1.35±2.53[a]
QoL	7.33±2.35	6.06±2.07	−1.28±1.93[a]	7.71±2.74	5.81±2.75	−1.90±1.90[a]
Total	20.11±7.63	15.11±6.93	−5.00±6.30[a]	21.23±9.38	15.39±7.87	−5.84±6.48[a]

Values are presented as mean±standard deviation.
IPSS, International Prostate Symptom Score; CPSI, Chronic Prostatitis Symptom Index; QoL, quality of life.
[a]:$p < 0.05$ between baseline and after treatment.

TABLE 3. Treatment outcome odds ratios, adjusted for age, prostate volume, IPSS, and category of CP/CPPS

Variable	Treatment outcome, OR (95% CI)[a]
Age ≥ 50 y	0.260 (0.034–1.978)
Prostate volume ≥ 30 mL	2.753 (0.546–13.883)
IPSS	
< 8	1
8–20	3.181 (0.222–45.580)
≥ 21	2.151 (0.122–37.886)
Category IIIB	1.825 (0.377–8.833)

IPSS, International Prostate Symptom Score; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; OR, odds ratio; CI, confidence interval.
[a]:Logistic regression.

DISCUSSION

CP/CPPS is a common disorder that is typically accompanied by pain with ejaculation or discomfort in the pelvic or perineal region with prominent lower urinary tract symptoms [6-8]. Although prostatic inflammation has been identified in many patients with this syndrome, the etiology and pathophysiology of CP/CPPS remain unknown [4-7].

The NIH consensus group identifies CP/CPPS on the basis of WBCs in the EPS, VB3, or semen without any evidence of uropathogenic bacteria detected by standard microbiological methodology [7,8]. The Meares-Stamey 4-glass test or simpler 2-glass test has been used to diagnosis CP [7]. Since Mobley reported the usefulness of a semen culture in combination with urine culture, the new NIH consensus classification is broader than the traditional approach, which was limited to the examination of EPS [6-9]. Krieger et al. [8] reported an increase in inflammation from 52% to 93% when the diagnosis was based on the addition VB3 and seminal fluid analysis (SFA) to EPS. In contrast, the NIH-CPCRN case-control study determined that seminal evaluation had little clinical value in differentiating prostatitis patients from normal controls [10]. In the present study, we did not perform SFA. In fact, most urologists rarely perform the 4-glass test and SFA in clinical practice. Potential reasons are that the test is not sensitive nor specific, the therapeutic predictive value is poor, and the test is relatively expensive, time-consuming, and quite uncomfortable for the patients [11,12].

Traditionally, patients with CP/CPPS receive empirical treatment. The most common treatments in clinical practice are antimicrobial agents and alpha-adrenergic receptor antagonists [13-15]. A European consensus report suggested that antibiotics are recommended for NIH category IIIA but not for NIH category IIIB [13]. However, Nickel et al. [2] found no significant differences between NIH category II, IIIA, and IIIB after antibiotic treatment. A recent prospective study showed that levofloxacin therapy was effective for CP/CPPS [14]. There are three reasonable explanations, as follows. First, the antimicrobial agent may have a placebo effect; second, the antimicrobial agent may eradicate noncultured microorganisms; and third, the antimicrobial agents may have immunosuppressive or anti-inflammatory effects [16]. Also, the treatment outcome was checked after 6 weeks, because this is the usual interval of treatment with an antimicrobial agent and it is generally believed that the bacterial organisms responsible for symptoms should be eradicated within this time [17].

Alpha-adrenergic receptor blockers are proven to be an effective treatment for benign prostatic hypertrophy. They inhibit the smooth muscle tone within the prostate gland and in the region of the bladder neck [3-5]. Presumably, these drugs are used empirically in the management of CP/CPPS because of overlapping pathogenesis, such as sympathetic over-activation [5,17]. A recent systemic review showed that alpha-adrenergic receptor blocker therapy was associated with significant improvement in CP/CPPS symptoms [18]. Moreover, antibiotics and alpha-blocker combination therapy was more effective than

monotherapy in treating CP/CPPS [14,18]. In this study, the combination alfuzosin and levofloxacin therapy resulted in significant improvements in both IPSS and NIH-CPSI scores. However, no significant difference in treatment outcome (improvements of at least 6 points or more on the NIH-CPSI total and domain scores) was observed between NIH category IIIA and IIIB. This suggests that a systemic approach other than NIH classification by the WBC count may be necessary.

In fact, our understanding of CP/CPPS has evolved with the development of the NIH classification. In our contemporary concept, CP/CPPS is not prostate-specific but incorporates other extraprostatic factors including pelvic muscle dysfunction, neurological disease, and psychiatric conditions [6-8]. Recently, Shoskes et al. [19] developed the clinical phenotyping system with six domain: urinary, psychosocial, organ specific, infection, neurologic/systemic, and tenderness (UPOINT), and a European study modified the clinical phenotyping system with an additional sexual dysfunction domain (UPOINTS) [20]. They showed that the number of positive domains correlated with symptom severity, and UPOINT-directed multimodal therapy improved symptoms and quality of life [21,22]. Therefore, because leukocytosis on EPS or VB3 and voiding symptoms only reveal organ-specific domains according to the UPOINT system, each patient should be assessed for not only laboratory findings such as a lower urinary tract localization test, but also the nature of symptoms. Although 51% of the patients showed clinical improvement in our study, there was no significant difference between NIH category IIIA and IIIB. This may reflect the heterogeneous aspect of CP/CPPS rather than the laboratory results.

As a result, we think that the NIH classification for CP/CPPS based on the presence or absence of WBCs in EPS, VB3, or semen is necessary as an initial diagnostic approach. However, from a therapeutic viewpoint, it has a limited role because of the multiple pathophysiologic factors that affect CP/CPPS.

There were limitations to this study. First, we used only EPS- and VB3-based classification. Krieger et al. [8] noted that semen analysis will increase the rate of detection of category IIIA. Therefore, if the semen analysis had been enforced in our study, more patients would have been diagnosed with IIIA. Second, the treatment outcome was measured only after 6 weeks. It may take a longer period of treatment before an improved symptom score is seen. Long-term follow-up is needed to support our results. Third, our study was designed as a retrospective review and had too small a number of cases to properly evaluate the impact of NIH classification on the outcomes of CP/CPPS. As such, a prospective randomized trial and long-term follow-up are needed.

CONCLUSIONS

CP/CPPS is a highly prevalent, multifactorial condition that affects men of all ages. The NIH classification provided useful information regarding potential etiologies and treatment in patients with CP/CPPS. However, the treatment response rate between NIH classification IIIA and IIIB was not significantly different after antibiotics and alpha-blockers combination treatment. Therefore, we think that factors other than inflammation also contribute to symptoms associated with CP/CPPS, and consideration of multiple phenotypes by use of UPOINT will help in the treatment of CP/CPPS.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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