

ORIGINAL CLINICAL ARTICLE

Comparison of cernitin pollen extract vs tadalafil therapy for refractory chronic prostatitis/chronic pelvic pain syndrome: A randomized, prospective study

Yoshihisa Matsukawa  | Yushi Naito | Yasuhito Funahashi | Shohei Ishida | Takashi Fujita | Kosuke Tochigi | Masashi Kato | Momokazu Gotoh

Department of Urology, Graduate School of Medicine, Nagoya University, Nagoya, Japan

Correspondence

Yoshihisa Matsukawa, MD, Department of Urology, Graduate School of Medicine, Nagoya University, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
Email: yoshi44@med.nagoya-u.ac.jp

Abstract

Aims: To compare the efficacy of cernitin pollen extract (cernitin) or tadalafil for treating persistent chronic pelvic pain despite α 1-blocker monotherapy in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and lower urinary tract symptoms (LUTS).

Methods: A total of 100 patients with refractory CP/CPPS despite ongoing α 1-blocker monotherapy were randomized to receive add-on therapy with either cernitin (4 capsules/day) or tadalafil (5 mg/d) for 12 weeks. At week 12, changes from baseline in the patients' CP/CPPS, LUTS, and voiding function, as assessed using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), the International Prostate Symptom Score (IPSS), and uroflowmetry, respectively, were compared between the groups.

Results: The final analysis included 42 and 45 patients in the cernitin and tadalafil groups, respectively. Although the NIH-CPSI total, NIH-CPSI pain sub-score, and NIH-CPSI quality of life sub-score significantly improved in both groups, the cernitin (vs tadalafil) group showed significantly greater improvements in the NIH-CPSI total score (-6.8 vs -4.6 ; $P = .02$) and NIH-CPSI pain sub-score (-4.1 vs -1.5 ; $P < .001$). Half (50%) of the patients in the cernitin group showed a reduction greater than 50% in their NIH-CPSI pain sub-score; in the tadalafil group, only four patients (8.9%) showed $\geq 50\%$ improvement ($P < .001$). In contrast, the improvement in LUTS was significantly superior in the tadalafil group.

Conclusion: Both cernitin and tadalafil significantly ameliorated chronic pelvic pain in patients with refractory CP/CPPS. The add-on of cernitin was more effective than tadalafil for pelvic pain and discomfort.

KEYWORDS

cernitin pollen extract, chronic pelvic pain syndrome, chronic prostatitis, chronic prostatitis symptom index, tadalafil

Abbreviations: BPH, benign prostatic hyperplasia; cernitin, cernitin pollen extract; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PVR, post-void residual urine volume; Qmax, maximum flow rate; QOL, quality of life; α 1-blocker, α 1-adrenoceptor antagonist.

1 | INTRODUCTION

A subset of patients with benign prostatic hyperplasia (BPH) have pelvic or perineal pain or discomfort suggestive of chronic prostatitis, in addition to lower urinary tract symptoms (LUTS), as prostatic inflammation is thought to play a key role in the pathogenesis and progression of BPH.¹ Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is classified as Category III prostatitis by the United States National Institutes of Health (NIH), and the condition is characterized by pelvic or perineal pain or painful voiding, in addition to LUTS including urgency, frequency, hesitancy, and poor interrupted flow.²⁻⁴ CP/CPPS is diagnosed when pelvic pain or discomfort is present for ≥ 3 months and other identifiable causes including active bacterial prostatic or urinary tract infection are ruled out.⁵ Since CP/CPPS has a significant negative impact on the patient's quality of life (QOL),⁶ the desire for treatment is high and effective treatment is required in clinical practice.

Anti-inflammatory medications, α_1 -adrenoceptor antagonists (α_1 blockers), and 5- α -reductase inhibitors are reported to be effective options for treating CP/CPPS-related voiding symptoms and pelvic pain in some clinical studies.⁷⁻⁹ In daily practice, α_1 blockers are often used for patients with CP/CPPS in addition to LUTS suggestive of BPH (LUTS/BPH); however, chronic pelvic pain and discomfort are more likely to be persistent and resistant to therapy using α_1 -blockers. A therapeutic strategy has not yet been established for patients who have residual pelvic or perineal pain despite α_1 -blocker monotherapy.

Phytotherapy, which is one of the traditional treatment options for CP/CPPS, is considered to be safe and effective for the relief from pelvic pain.^{7,10} In particular, cernitin pollen extract (cernitin) has been reported to improve chronic pelvic pain significantly over a 12-week period in a placebo-controlled randomized trial.¹¹ Meanwhile, tadalafil, the only PDE5 inhibitor approved for patients with LUTS/BPH, is reported to have multiple actions, including suppression of inflammation by the downregulation of Rho-kinase activity, which is expected to be useful for the treatment of CP/CPPS.¹² Several basic studies have reported that tadalafil significantly suppressed pelvic pain and prostatic inflammation in a nonbacterial prostatitis rat model.^{13,14}

It is of clinical interest to determine whether these old and new drugs, cernitin and tadalafil, respectively, can improve chronic pain or discomfort of the pelvic, perineal, scrotal, or phallic area in patients with CP/CPPS. To the best of our knowledge, no randomized controlled studies have compared the improvement in chronic prostatitis symptoms, such as chronic pelvic pain, in patients treated with one of these medications. Therefore, the aim of the present study was to compare the efficacy

of treatment with cernitin or tadalafil on not only LUTS, but also pelvic pain or discomfort, in patients with persistent CP/CPPS despite α_1 -blocker monotherapy.

2 | MATERIALS AND METHODS

This was a single-center, open label, and randomized controlled trial. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by our hospital's ethics committee (Institutional Review Board Approval number: 2017-0136). The study is registered at the UMIN Clinical Trials Registry.

2.1 | Patients

The study included men who had LUTS in addition to CP/CPPS at the first visit and who had persistent chronic prostatitis symptoms such as perineal and/or pelvic discomfort and/or pain despite α_1 -blocker monotherapy for 12 weeks or more between July 2017 and December 2018. The inclusion criteria were as follows: age ≥ 45 years; National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI)^{5,15} pain sub-score ≥ 4 ; total International Prostate Symptom Score (IPSS) ≥ 8 ; the culture of a urine specimen collected after a prostate massage (VB3) was negative; and prostate volume ≥ 20 mL, as determined by transabdominal ultrasonography. Patients were excluded if they had a bacterial prostatitis, an active urinary tract infection, neurogenic bladder dysfunction, or bladder calculi; had received oral treatment with PDE5 inhibitors, cernitin pollen extract, nitroglycerin, amyl nitrite, or isosorbide dinitrate within 12 weeks before study entry; and/or had severe cardiac disease, renal dysfunction (serum creatinine level ≥ 3 mg/dL), or hepatic dysfunction (aspartate and alanine aminotransferase concentrations three times greater than the normal values).

Patients who satisfied all inclusion criteria and displayed none of the exclusion criteria were randomized to either the cernitin group, which received cernitin pollen extract (4 capsules/d), or the tadalafil group, which received tadalafil (5 mg/d). The α_1 -blocker that was taken orally before study entry continued to be administered during this study. Randomization was performed using a random number table.

2.2 | Assessment and endpoints

The NIH-CPSI was assessed before randomization and at 12 weeks after add-on treatment to evaluate changes in chronic prostatitis symptoms. The same schedule was

implemented to evaluate LUTS and voiding functions via IPSS and uroflowmetry (UFM). The maximum flow rate (Qmax), voided volume, and post-void residual urine volume (PVR) on UFM were assessed as parameters of voiding function.

The primary endpoint was defined as the change from baseline to week 12 in the NIH-CPSI total score and NIH-CPSI pain sub-score. As secondary endpoints, the change in NIH-CPSI urinary sub-score, NIH-CPSI QOL sub-score, IPSS, and voiding parameters on UFM were evaluated.

2.3 | Sample size calculation

Regarding the target enrollment number, the expected mean improvement in the NIH-CPSI pain sub-score from the baseline during cernitin or tadalafil treatment was set to be 4.5 points and 3.0 points, respectively. Additionally, the standard deviation of the NIH-CPSI pain sub-score change between the two groups was assumed to be 2.0. Thus, we determined that the sample size required for determining this difference was 40 patients in each group, when the two-sided significance level and power were assumed to be 5% and 80%, respectively. To account for an estimated 20% dropout rate, 50 patients were required in each group for evaluation. Patients were excluded from the analysis if they discontinued treatment due to adverse reactions or if subjective assessment data such as the NIH-CPSI questionnaire were not collected at 12 weeks of treatment.

2.4 | Statistical analysis

All statistical values are represented as the mean \pm standard deviation (SD) or median and interquartile

range (IQR), based on whether or not the data were normally distributed. A the Wilcoxon signed-rank test or Paired *t*-test was performed to evaluate the therapeutic effects before and after treatment in each group. Additionally, Mann-Whitney *U* tests, Welch's *t*-tests, McNemar tests, and χ^2 tests were performed to compare the changes in subjective symptoms and objective findings between the two groups. All tests were two-tailed, and differences were considered significant at $P < .05$. All statistical analyses were performed using SPSS software (IBM, Armonk, NY).

3 | RESULTS

The CONSORT flow diagram was shown in Figure 1. In total, 100 patients (50 patients each) were randomly allocated into the cernitin and tadalafil groups. Of the 50 patients in each group, treatment was discontinued owing to adverse effects in one (2.0%) patient in the cernitin group (constipation [$n = 1$]) and three (6.0%) patients in the tadalafil group (headache [$n = 2$] and erection problems [$n = 1$]). No significant difference in the incidence of adverse effects was found between the groups. Additionally, three patients (6.0%) in the cernitin group and two patients (4.0%) in the tadalafil group withdrew for unknown reasons. The evaluation of subjective symptoms, including completion of the NIH-CPSI questionnaire, was not performed after treatment for four patients in the cernitin group. Therefore, the final analysis included 42 patients in the cernitin group (mean age, 65.9 years; range, 46-81 years) and 45 patients in the tadalafil group (mean age, 67.9 years; range, 48-82 years). The demographic and clinical information of the patients in each group at baseline is shown in Table 1. No significant differences in age, prostate volume, serum prostate specific antigen (PSA) level, or

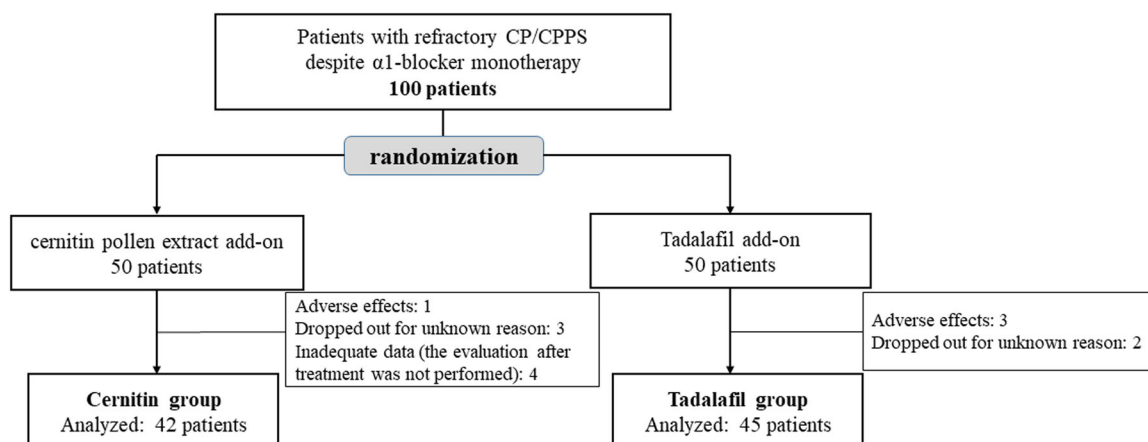


FIGURE 1 CONSORT flow diagram

TABLE 1 Background between the two groups

	Cernitin group	Tadalafil group	
	Mean + SDn	Mean + SDn	
N	42	45	P
Age, y	65.9 ± 9.9	67.9 ± 6.9	.62
45-49	4	2	
50-59	5	7	
60-69	17	18	
70-79	13	17	
80-	3	1	
Prostate volume, mL	34.6 ± 10.1	37.2 ± 10.5	.23
≥20-<35	27	23	
≥35-<50	10	17	
≥50	5	5	
PSA, ng/mL			
Baseline	2.21 ± 2.31	2.34 ± 1.58	.74
12 wk	2.01 ± 2.33	2.32 ± 1.48	.47
Period of α1-blocker monotherapy, mo	4.8 ± 1.6	4.9 ± 1.9	.93

Abbreviation: PSA, prostate specific antigen.

duration of α1-blocker monotherapy were detected between the groups at baseline.

The changes in subjective symptoms from baseline to 12 weeks after the start of cernitin or tadalafil treatment are summarized in Table 2. No significant differences in IPSS, IPSS-voiding sub-score, IPSS-storage sub-score, NIH-CPSI total score, or NIH-CPSI sub-score were detected between the groups at baseline. Compared to the baseline scores, significant decreases (improvements) in the NIH-CPSI total score, NIH-CPSI pain sub-score, and NIH-CPSI QOL sub-score were observed at week 12 in both groups. The improvements in the NIH-CPSI total and NIH-CPSI pain sub-scores were significantly greater in the cernitin group than in the tadalafil group. The mean NIH-CPSI total changed from 19.6 to 12.8 in the cernitin group and from 19.7 to 15.1 in the tadalafil group. The percentage of patients who demonstrated $a \geq 25\%$ improvement in NIH-CPSI total, which is considered to be clinically meaningful, was significantly higher in the cernitin group than in the tadalafil group (76.2% vs 48.9%; $P = .008$). The mean beneficial change in the NIH-CPSI pain sub-score was significantly higher in the cernitin group than in the tadalafil group (4.1 vs 2.4; $P < .001$; 95% CI, 1.7 to 3.6; Figure 2). Although 27 patients (64.3%) in the cernitin group still had persistent CPPS symptoms (NIH-CPSI pain sub-score of 4 or more) after 12 weeks of add-on treatment, 21 patients (50.0%) of the 42 demonstrated a greater than 50% reduction in the

NIH-CPSI pain sub-score after administration. On the other hand, in the tadalafil group, 41 patients (91.1%) still had persistent CPPS symptoms after 12 weeks of add-on treatment, and only four patients (8.9%) showed $\geq 50\%$ improvement in the NIH-CPSI pain sub-score. The percentage of patients who demonstrated $a \geq 50\%$ improvement in the NIH-CPSI pain sub-score was significantly higher in the cernitin group than in the tadalafil group ($P < .001$). In contrast, the NIH-CPSI urinary sub-score significantly decreased (improved) only in the tadalafil group. Regarding change of IPSS, significant decreases (improvements) in the total IPSS, IPSS-storage, and IPSS-QOL scores were observed at week 12 in the tadalafil group. Meanwhile, in the cernitin group, the IPSS-QOL and IPSS-voiding sub-score significantly improved, whereas no significant improvement was seen in the IPSS-total and IPSS-storage sub-scores. The improvement in the IPSS-storage sub-score in the tadalafil group was significantly superior to that in the cernitin group.

The changes in the voiding parameters on UFM between the two groups are summarized in Table 3. The mean Qmax improved from 9.7 to 10.8 mL/s in the cernitin group and from 9.3 to 11.2 mL/s in the tadalafil group. Only the improvement in the tadalafil group was statistically significant, although there was no significant difference in the improvement of Qmax between the groups. The voided volume and PVR slightly improved in both groups; however, these changes were not statistically significant.

4 | DISCUSSION

This was, to our knowledge, the first study to compare the efficacy of two drugs, cernitin and tadalafil, on chronic pelvic pain, along with LUTS, in patients with persistent CP/CPPS despite α1-blocker monotherapy. We found that cernitin treatment, compared with tadalafil treatment, had a superior ameliorating effect on chronic prostatitis symptoms such as pelvic pain and discomfort, although the improvement in LUTS, especially storage symptoms, was greater following tadalafil treatment. These findings may provide clinicians with an evidence-based strategy in selecting a medical treatment for the subgroup of patients with persistent chronic prostatitis despite ongoing α1-blocker monotherapy, who are frequently encountered in clinical practice.

Cernitin pollen extract contains 63 mg of the defined pollen extract fractions Cernitin T60 (water-soluble fraction) and Cernitin GBX (fat-soluble fraction). Kamiyo et al reported that cernitin pollen extract protected

TABLE 2 Changes in parameters related to LUTS and chronic prostatitis between the two groups

	Cernitin group		Tadalafil group		
	42	P (intra-group)	45	P (intra-group)	P (intergroup)
N	Mean ± SD	(95% CI)	Mean ± SD	(95% CI)	(95% CI)
NIH-CPSI total					
Baseline	19.6 ± 5.9		19.7 ± 4.6		.90
12 wk	12.8 ± 5.2	<.001	15.1 ± 4.7	<.001	
Mean beneficial change	6.8 ± 3.9	(4.3 to 9.2)	4.6 ± 4.4	(2.6 to 6.5)	.02 (0.4 to 3.9)
NIH-CPSI pain					
Baseline	8.5 ± 2.5	<.001	8.2 ± 2.8		.53
12 wk	4.4 ± 2.3		6.7 ± 2.9	.02	
Mean beneficial change	4.1 ± 2.4	(3.1 to 5.2)	1.5 ± 2.1	(0.3 to 2.7)	<.001 (1.7 to 3.6)
NIH-CPSI urinary					
Baseline	4.3 ± 2.3		4.5 ± 1.4		.64
12 wk	3.7 ± 1.9	.19	3.0 ± 1.3	<.001	
Mean beneficial change	0.6 ± 1.3	(−0.3 to 1.5)	1.4 ± 1.4	(0.8 to 2.0)	.008 (−1.4 to −0.2)
NIH-CPSI QOL					
Baseline	6.8 ± 2.2		7.0 ± 1.6		.45
12 wk	4.7 ± 2.3	<.001	5.3 ± 2.2	<.001	
Mean beneficial change	2.0 ± 1.7	(1.0 to 3.0)	1.8 ± 2.2	(1.0 to 2.6)	.57 (−0.6 to 1.1)
IPSS					
Baseline	16.5 ± 6.2		16.8 ± 4.5		.85
12 wk	14.0 ± 6.4	.06	12.2 ± 5.2	<.001	
Mean beneficial change	2.6 ± 5.1	(−0.2 to 5.3)	4.5 ± 4.3	(2.5 to 6.6)	.06 (−4.0 to 0.1)
IPSS-voiding					
Baseline	10.0 ± 4.3		9.9 ± 3.5		.90
12 wk	8.0 ± 4.1	.03	7.2 ± 3.8	.001	
Mean beneficial change	2.0 ± 3.5	(0.1 to 3.8)	2.6 ± 3.6	(1.1 to 4.2)	.38 (−2.2 to 0.8)
IPSS-storage					
Baseline	6.5 ± 2.9	.35	6.9 ± 2.6		.58
12 wk	6.0 ± 2.9		5.0 ± 2.4	<.001	
Mean beneficial change	0.6 ± 2.3	(−0.7 to 1.9)	1.9 ± 2.3	(−0.9 to 3.0)	0.01 (−2.3 to −0.3)
IPSS-QOL					
Baseline	4.3 ± 1.0		4.4 ± 0.8		.46
12 wk	3.4 ± 1.1	<.001	3.1 ± 1.3	<.001	
Mean beneficial change	0.9 ± 0.9	(0.4 to 1.4)	1.3 ± 1.4	(0.9 to 1.8)	.08 (−1.0 to 0.1)

Abbreviations: CI, confidence interval; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; QOL, quality of life; SD, standard deviation.

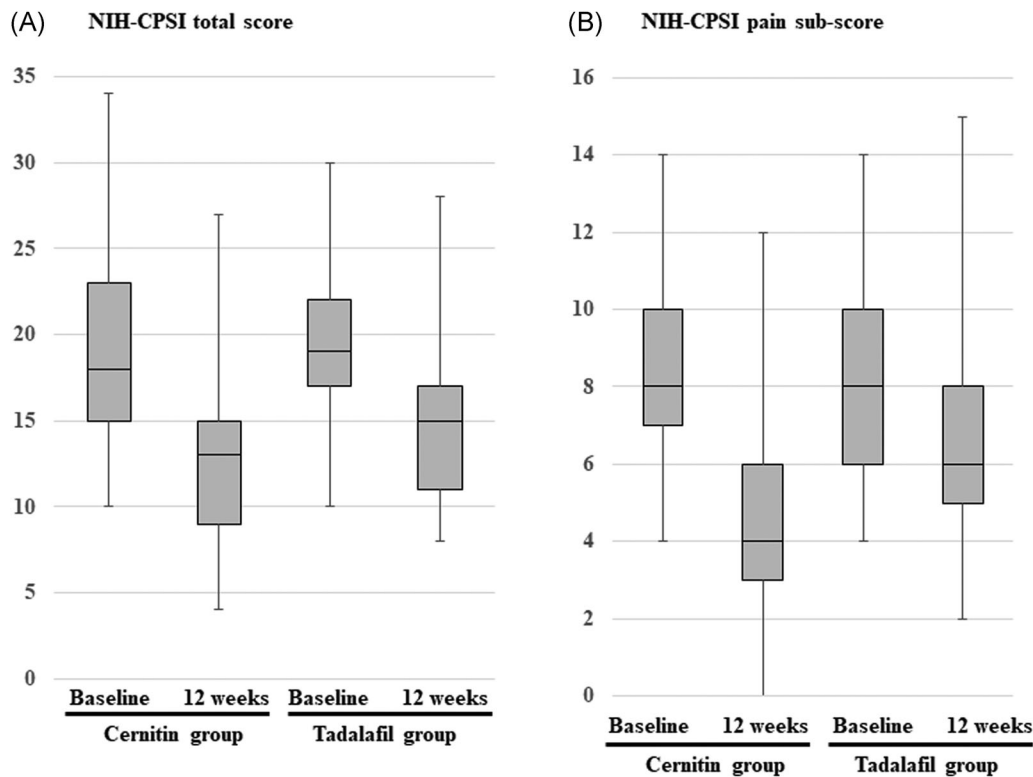


FIGURE 2 Change in the NIH-CPSI total score A, and NIH-CPSI pain sub-score B, in the cernitin and tadalafil groups. Significant decreases (improvements) in the NIH-CPSI total score and NIH-CPSI pain sub-score were observed at week 12 in both groups. In the comparison between the groups, the improvement of these parameters was significantly greater in the cernitin group

acinar epithelial cells, mainly via the action of GBX, and also inhibited stromal proliferation in association with enhanced apoptosis, mainly via the action of T-60, in a rat model with nonbacterial prostatitis.¹⁶ Wagenlehner et al¹¹ conducted a multicenter, prospective, randomized, double-blind, placebo-controlled phase 3 clinical study comparing the effects of cernitin pollen extract treatment to a placebo in men with CP/CPPS (NIH IIIA). After 12 weeks of treatment, the mean changes from baseline in the NIH-CPSI total score and pain domain score were -8.72 and 4.93 , respectively, in the cernitin group; and -4.77 and -2.79 , respectively, in the placebo group. They concluded that cernitin significantly improved NIH-CPSI total symptoms, pain, and QOL in patients with CP/CPPS without severe side effects, compared to the placebo treatment. Additionally, Cai et al¹⁷ reported that a significantly greater improvement in the NIH-CPSI pain domain was seen in a cernitin pollen extract-treated group (mean change, -4.36) compared with an ibuprofen-treated group (mean change -2.22) of patients with CP/CPPS. In our study, the mean beneficial changes in the NIH-CPSI total score and NIH-CPSI pain sub-score following cernitin treatment were 6.8 and 4.1 , respectively, and thus, the degree of improvement in these parameters was comparable to those in previous reports.

Few studies have focused on the effect of tadalafil on chronic prostatitis symptoms in patients with CP/CPPS, although PDE5 inhibitors including tadalafil have been reported to suppress prostate inflammation, fibrosis, and hypo-oxygenation in rabbits fed a high fat diet and to suppress pelvic pain by improving inflammatory changes in an experimental autoimmune prostatitis rat model.^{13,14,18,19} In clinical practice, Benelli et al²⁰ reported that tadalafil significantly improved the NIH-CPSI total score, as well as scores for the pain domain, urinary domain, and QOL domain in 14 patients with CP/CPPS, although they found that the Qmax and PVR in UFM did not improve. In particular, the mean NIH-CPSI pain sub-score decreased from 13.7 to 1.6 after 12 weeks of tadalafil administration, and this change is considered to be noteworthy. Hiramatsu et al²¹ reported that 12 weeks of tadalafil treatment was significantly effective in alleviating not only LUTS, but also pelvic pain in 24 patients with both LUTS/BPH and severe CP/CPPS (NIH-CPSI pain sub-score ≥ 4). In their study, the mean beneficial changes in the IPSS, NIH-CPSI total, and NIH-CPSI pain sub-scores were 8.5 , 10.0 , and 4.4 , respectively. In contrast, in our study, the changes in these parameters were 4.5 , 4.6 , and 1.5 , respectively, although these changes were statistically significant. In our study, patients with refractory chronic prostatitis symptoms of both LUTS/BPH and CP/CPPS despite $\alpha 1$ -blocker

TABLE 3 Changes in voiding parameters between the two groups

N	Cernitin group 42		Tadalafil group 45		
	Mean \pm SD or median (IQR)	P (intra-group) (95% CI)	Mean \pm SD or median (IQR)	P (intra-group) (95% CI)	P (inter-group) (95% CI)
Qmax, mL/s					
Baseline	9.7 \pm 3.9		9.3 \pm 3.6		.61
12 wk	10.8 \pm 3.8	.17	11.2 \pm 3.9	.02	
Mean beneficial change	1.1 \pm 4.2	(−0.5 to 2.8)	1.9 \pm 3.3	(0.3 to 3.5)	.38 (−2.4 to 0.9)
Voided volume, mL					
Baseline	159 \pm 71		143 \pm 61		.24
12 wk	171 \pm 100	.55	164 \pm 73	.14	
Mean beneficial change	12 \pm 118	(−27 to 50)	21 \pm 88	(−7 to 49)	.68 (−54 to 36)
PVR, mL					
Baseline	30 (14-50)		30 (15-70)		.25
12 wk	20 (10-40)	.15	30 (15-60)	.12	
Beneficial change	5 (−10 to 20)		6 (−10 to 20)		.98

Abbreviations: CI, confidence interval; IQR, interquartile range; PVR, post-void residual urine volume; SD, standard deviation.

monotherapy for 12 weeks or more were included. The differences in patient backgrounds, such as the higher proportion of patients with refractory CP/CPPS in our study, could affect these results, although we were unable to identify a precise explanation for the differences in the effects of tadalafil on IPSS and CP/CPPS symptoms between these studies.

In addition, the detailed mechanisms underlying the significantly greater efficacy of cernitin than that of tadalafil in the improvement in chronic pelvic pain remains incompletely understood, but we can offer a plausible hypothesis. Although few studies have focused on the association between the inflammatory suppression of prostate tissue and the alleviation of pelvic pain, the suppression of chronic prostatic inflammation may contribute to the improvement of chronic pelvic pain and discomfort.²² When comparing the beneficial effects of the two drugs on prostate inflammation, cernitin might suppress inflammation more effectively in prostate tissue than tadalafil. Togo et al²³ reported that oral administration of cernitin for 30 days significantly reduced the mean serum PSA level by 0.6 ng/mL (mean reduction of 7.6%). Meanwhile, to our knowledge, there has been no report demonstrating that tadalafil reduced the serum PSA level in patients with LUTS/BPH and/or CP/CPPS. In our study, the mean serum PSA level changed from 2.21 to 2.01 ng/mL in the cernitin group and from 2.34 to 2.32 ng/mL in the tadalafil group. The decrease in PSA was significant only in the cernitin group (mean reduction of 9.1%, $P < .001$). Generally, serum PSA is considered to be a useful marker of prostatic inflammation in

addition to prostate cancer, and the difference in serum PSA reduction between the two drugs may suggest a differential suppressive effect on chronic inflammation of prostate tissue.

The present study has several limitations. First, we evaluated the therapeutic effect for CP/CPPS using only the NIH-CPSI questionnaire response. Therefore, placebo effects cannot be completely excluded in terms of subjective symptom changes. However, these effects were likely be equal between the two groups and were not likely to have affected the comparison of the therapeutic effects for CP/CPPS between the two groups. Second, per-protocol analysis was performed in this study, and patients who deviated from the protocol were excluded from this analysis, which may have led to an attrition bias. However, the dropout rate was low and did not differ between the two groups; thus the effect of patients dropping out was considered to be small. Third, this comparative study targeted only men and the effect of these medical agents for women with chronic pelvic pain-related conditions such as painful bladder syndrome is unknown. Finally, the follow-up period was only 12 weeks. Since pharmacotherapy for CP/CPPS should generally be continued for a longer period, long-term comparisons of the efficacy of these therapies need to be performed in future studies.

5 | CONCLUSIONS

This comparative study showed that both cernitin and tadalafil significantly improved chronic pelvic pain in

patients with refractory CP/CPPS (NIH category IIIA and IIIB) despite α 1-blocker monotherapy. The add-on of cernitin was more effective than tadalafil for pelvic pain and discomfort, which are pathognomonic symptoms in CP/CPPS, although the improvement of LUTS such as storage symptoms was significantly superior for the add-on treatment with tadalafil.

ACKNOWLEDGMENTS

The authors would like to acknowledge all patients for participating and all trial investigators for their contribution to the data acquisition and patient care.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study before enrollment. The study's protocol was approved by Nagoya University's Graduate School of Medicine's ethics committee (Institutional Review Board Approval number: 2017-0136). The study was registered at the UMIN clinical trials registry (<https://center.umin.ac.jp>) as UMIN000027420.

ORCID

Yoshihisa Matsukawa  <http://orcid.org/0000-0001-7823-2600>

REFERENCES

- Gandaglia G, Briganti A, Gontero P, et al. The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH). *BJU Int.* 2013;112:432-441.
- Schaeffer AJ. Clinical practice. Chronic prostatitis and the chronic pelvic pain syndrome. *N Engl J Med.* 2006;355:1690-1698.
- Schaeffer AJ, Datta NS, Fowler JE Jr, et al. Overview summary statement. Diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). *Urology.* 2002;60:1-4.
- Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. *JAMA.* 1999;282:236-237.
- Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. *Urology.* 1999;54:229-233.
- Walz J, Perrotte P, Hutterer G, et al. Impact of chronic prostatitis-like symptoms on the quality of life in a large group of men. *BJU Int.* 2007;100:1307-1311.
- Franco JVA, Turk T, Jung JH, et al. Pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrane systematic review. *BJU Int.* 2020;125:490-496.
- Rees J, Abrahams M, Doble A, Cooper A. Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. *BJU Int.* 2015;116:509-525.
- Shoskes DA, Nickel JC, Rackley RR, Pontari MA. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. *Prostate Cancer Prostatic Dis.* 2009;12:177-183.
- Rees J, Abrahams M, Doble A, Cooper A. Diagnosis and treatment of chronic bacterial prostatitis and chronic prostatitis/chronic pelvic pain syndrome: a consensus guideline. *BJU Int.* 2015;116:509-525.
- Wagenlehner FM, Schneider H, Ludwig M, Schnitker J, Brähler E, Weidner W. A pollen extract (Cernilton) in patients with inflammatory chronic prostatitis-chronic pelvic pain syndrome: a multicentre, randomised, prospective, double-blind, placebo-controlled phase 3 study. *Eur Urol.* 2009;56:544-551.
- Andersson KE, de Groat WC, McVary KT, et al. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism (s) of action. *Neurourol Urodyn.* 2011;30:292-301.
- Kurita M, Yamaguchi H, Okamoto K, Kotera T, Oka M. Chronic pelvic pain and prostate inflammation in rat experimental autoimmune prostatitis: effect of a single treatment with phosphodiesterase 5 inhibitors on chronic pelvic pain. *Prostate.* 2018;78:1157-1165.
- Sugimoto M, Zhang X, Ueda N, et al. A phosphodiesterase 5 inhibitor, tadalafil, suppresses stromal predominance and inflammation in a rat model of nonbacterial prostatitis. *BMC Urol.* 2019;19:99.
- Litwin MS, McNaughton-Collins M, Fowler FJ Jr, et al. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. *J Urol.* 1999;162:369-375.
- Kamijo T, Sato S, Kitamura T. Effect of cernitin pollen-extract on experimental nonbacterial prostatitis in rats. *Prostate.* 2001;49:122-131.
- Cai T, Wagenlehner FM, Luciani LG, et al. Pollen extract in association with vitamins provides early pain relief in patients affected by chronic prostatitis/chronic pelvic pain syndrome. *Exp Ther Med.* 2014;8:1032-1038.
- Morelli A, Comeglio P, Filippi S, et al. Mechanism of action of phosphodiesterase type 5 inhibition in metabolic syndrome-associated prostate alterations: an experimental study in the rabbit. *Prostate.* 2013;73:428-441.
- Okamoto K, Kurita M, Yamaguchi H, Numakura Y, Oka M. Effect of tadalafil on chronic pelvic pain and prostatic inflammation in a rat model of experimental autoimmune prostatitis. *Prostate.* 2018;78:707-713.
- Benelli A, Mariani S, Varca V, Gregori A, Barrese F, Cappa M. Once-daily 5 mg tadalafil oral treatment for patients with chronic prostatitis/chronic pelvic pain syndrome. *Ther Adv Urol.* 2018;10:377-381.
- Hiramatsu I, Tsujimura A, Soejima M, et al. Tadalafil is sufficiently effective for severe chronic prostatitis/chronic pelvic

- pain syndrome in patients with benign prostatic hyperplasia. *Int J Urol*. 2020;27:53-57.
22. Nickel JC. Is chronic prostatitis/chronic pelvic pain syndrome an infectious disease of the prostate? *Investig Clin Urol*. 2017; 58:149-151.
23. Togo Y, Ichioka D, Miyazaki J, et al. Japanese Research Group for Urinary Tract Infection (. Oral administration of cernitin pollen extract (Cernilton®) for 30 days might be useful to avoid unnecessary biopsy in prostate biopsy candidates: a preliminary study. *Int J Urol*. 2018;25:479-485.

How to cite this article: Matsukawa Y, Naito Y, Funahashi Y, et al. Comparison of cernitin pollen extract vs tadalafil therapy for refractory chronic prostatitis/chronic pelvic pain syndrome: A randomized, prospective study. *Neurourology and Urodynamics*. 2020;1–9.
<https://doi.org/10.1002/nau.24454>