

The Effects of Transrectal Radiofrequency Hyperthermia on Patients With Chronic Prostatitis and the Changes of MDA, NO, SOD, and Zn Levels in Pretreatment and Posttreatment

Mingdong Gao, Hui Ding, Ganping Zhong, Jianzhong Lu, Hanzhang Wang, Qinfang Li, and Zhiping Wang

OBJECTIVE	To assess the effect of transrectal radiofrequency hyperthermia (TRFH) in 159 patients with chronic prostatitis (CP) and explore the changes of reactive oxygen species in CP patients pretreatment and posttreatment.
METHODS	Patients diagnosed with CP were randomized to 6 weeks of tamsulosin plus clarithromycin, TRFH, or TRFH with tamsulosin plus clarithromycin group. The primary outcome measure was evaluated by the National Institutes of Health Chronic Prostatitis Symptom Index. Malondialdehyde (MDA), superoxide dismutase (SOD), and nitrogen monoxide (NO) were measured by biochemical assay. Zinc (Zn) content was assayed by atomical spectrophotography.
RESULTS	All 105 patients in the TRFH or TRFH with tamsulosin plus clarithromycin group showed statistically significant improvement of pain, quality of life, and micturition domains compared with the tamsulosin plus clarithromycin group. Regardless of type IIIa or type IIIb CP, there was a significant improvement in the TRFH or TRFH with tamsulosin plus clarithromycin group compared with tamsulosin plus clarithromycin group ($P < .05$). Compared with pretreatment, MDA, NO, and Zn were decreased in type II and IIIa, whereas SOD was only increased significantly in type II ($P < .05$).
CONCLUSION	Our study reveals TRFH as an effective therapy option for CP, especially type IIIa or type IIIb CP. The results of TRFH with tamsulosin plus clarithromycin group was superior to the TRFH group or the tamsulosin plus clarithromycin group alone. In comparison with pretreatment, differences in reactive oxygen species levels and Zn in CP patients suggest that these factors could be used as a biomarker to evaluate the symptoms of CP and the effects of treatment. UROLOGY 79: 391–396, 2012. © 2012 Published by Elsevier Inc.

Chronic bacterial prostatitis is associated with recurrent lower urinary tract infections secondary to areas of focal uropathogenic bacteria residing in the prostate gland or to chronic pelvic pain syndrome (CPPS) and is characterized by pelvic or perineal pain with or without detectable inflammatory changes in the prostate tissue and secretions. It is the most common urological diagnosis in men younger than 50 years of age, yet little is known about its cause and pathogenesis.¹ No

causal or standardized treatment is available at present. Therefore, the effective treatment options have become increasingly important.

Heat therapy has been delivered transrectally and transurethally using different energy sources, including interstitial heat, microwave, low-level radiofrequency energy, and laser. Furthermore, each mode of therapy used differs by target temperature. Transrectal procedures reported target temperatures of 41–45°C, whereas the transurethral procedures reported temperatures of 45–60°C.² Although a number of investigators have documented favorable outcomes, the data presented are difficult to interpret. This is primarily because of inconsistencies in outcome measures, modalities of treatment, and study design. Furthermore,

From the Institute of Urology and Department of Urology, the Second Hospital of Lanzhou University, Lanzhou, China

Reprint requests: Zhiping Wang, Ph.D., M.D., Institute of Urology, the Second Hospital of Lanzhou University, 80 Cui YingMeng Street, Lanzhou, Gansu, 730000, China. E-mail: erylwzp@lzu.edu.cn

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the presumed mechanism of action of these therapies is unclear and only few studies have been performed that address this issue.

Oxygen-free radicals (OFR) that cause tissue damage by lipid peroxidation (LPO)³ include mainly superoxide anion (O₂⁻), hydrogen peroxide (H₂O₂), hydroxy free radical (-OH), and nitrogen monoxide (NO). LPO has yielded several types of secondary free radicals and a large number of reactive compounds, including malondialdehyde (MDA), resulting in the destruction of the cellular portion. Cells are equipped with various antioxidants, such as vitamins E and C, glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and so on. These can scavenge supernumerary OFR and protect an organism from the cytotoxic effects of OFR.^{4,5} Zinc (Zn) content in prostatic secretion and semen was higher than in other organs and body fluids, and high levels of prostatic Zn were associated with prostatic antimicrobial activities and are depressed in patients with chronic prostatitis, which showed that Zn played an important role in keeping function of prostate.^{6,7} Further description of prostate reactive oxygen species (ROS) and Zn may help to characterize the different types of chronic prostatitis (CP) and improve our understanding of the mechanism of the prostate heat therapy in patients with CP. In the present study, we investigated the effects of transrectal radiofrequency hyperthermia and we measured the levels of representative ROS and Zn at pretreatment and posttreatment.

MATERIAL AND METHODS

Subjects

We collected 159 cases of chronic prostatitis patients. All fulfilled the National Institutes of Health (NIH) diagnostic criteria⁸ for CP. The National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI) score was determined for each patient by the carefully completed NIH-CPSI questionnaires.

Subjects were recruited to our clinic between January 10, 2008 and March 30, 2009. The study protocol was approved by the ethical committee of the Lan Zhou University. All participants provided written, informed consent.

Inclusion Criteria and Exclusion Criteria

Inclusion criteria were (1) men who were at least 18 years of age and who had been seen by a physician for symptoms of chronic prostatitis within the previous 3 months, (2) pain or discomfort in the pelvic region for at least 6 weeks and a total score of at least 12 on the NIH-CPSI.

Exclusion criteria were (1) urinary tract infection; (2) acute bacterial at study entry (bacteriuria $\geq 10^4$ cfu/mL in midstream urine [VB2] or $\geq 10^3$ cfu/mL in VB3); (3) history of urethritis, with discharge 4 weeks before study entry; (4) a history of epididymitis or sexually transmitted infection (STI); (5) residual urine volume >50 mL resulting from bladder outlet obstruction (BOO) by urodynamic examination; (6) indication for or history of prostate surgery, including prostate biopsy; (7) history of urogenital cancer; (8) neurologic disease affecting the bladder; (9) treatment with phytotherapeutic agents, α -blocker

agents, or antimicrobial substances with prostatic penetration 4 weeks before study entry; (10) treatment with agents influencing intraprostatic hormone metabolism 6 months before study entry; and (11) unmarried or with no children.

Study Design

One-hundred fifty-nine patients were randomly divided into 3 treatment groups based on the order of their arrival, respectively: Group I received tamsulosin 0.2 mg once daily and clarithromycin 0.25 g twice daily for 6 weeks; group II underwent a 60-min treatment with transrectal radiofrequency hyperthermia (TRFH, ZRL-II-A cavity intervention treatment instrument was provided by Shanghai Songhang Industry, Co., Ltd. [Shanghai, China], temperature 40–43°C) every day for 5 days; and group III received transrectal radiofrequency hyperthermia combined with tamsulosin plus clarithromycin.

Efficacy Assessment

We evaluated the efficacy of transrectal radiofrequency hyperthermia according to the symptomatic improvement in the pain, micturition, and quality of life (QoL) domains of the NIH-CPSI. In addition, qualitative efficacy parameters based on NIH-CPSI—namely, improvement of NIH-CPSI summary score by $\geq 25\%$ and improvement of NIH-CPSI summary score by at least 6 points—were introduced as recommended by Nickel et al.⁹

Expressed Prostatic Secretion, Semen Collection, and Examination

Expressed prostatic secretion (EPS) samples were collected after 3 days' abstinence. The penis and meatus were cleaned and disinfected. Urine was collected before and after prostate massage for routine examination and bacterial culture. EPS was smeared on a glass slide and examined promptly with a high-power microscope (400x) for cells and lecithin bodies. The average number of white blood cells in 5 high-power fields (WBC/hpf) was recorded.

The semen samples were collected by patients in a private room near laboratories after they washed their glans penis with soap and water. The semen samples were obtained by masturbation after urinating and were ejaculated into a sterile collection tube. After ejaculation, the semen was incubated at 37°C for 25–45 minutes for liquefaction.¹⁰

Measurements of ROS and Zn Levels

Seminal MDA content was determined by the thiobarbituric acid (TBA) method¹¹ and the TBA reactivity was measured spectrophotometrically at 534 nm by UV-Vis spectrophotometer UV9200; the NO concentration was estimated by a method of the nitrate reductase, and SOD activity was measured as the inhibition of nitroblue tetrazolium reduction caused by superoxide anion generation by xanthine plus xanthine oxidase (Bio-engineering, Co, Ltd., Nanjing, China, <http://www.njjcbio.com/>). Zn content was measured by atomic spectroscopy AA6800.

Statistical Analysis

Values are reported as mean \pm SD. Data were analyzed with statistical software SPSS (version 13.0 for Windows, SPSS Inc., Chicago, IL). Comparison within groups was evaluated by paired-samples *t*-test, and comparison among groups was assessed by 2 independent samples *t*-test. The partial correlation

Table 1. The baseline characteristics and changes of ROS index, Zn²⁺ in pre- and posttreatment for the different subtypes of CP in 3 groups (mean ± SD)

Categories	Type II (54)		Type IIIa (53)		Type IIIb (52)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Group I (n)	16		14		16	
Rate of efficacy (%)	41.2		60		60.9	
Age, y (mean)	34.6		35.9		36.7	
Duration of disease (mos)	9.8		17.1		20.9	
NIH-CPSI	21.2 ± 4.1	15.9 ± 3.9	20.9 ± 2.9	14.6 ± 3.4	20.2 ± 4.6	14.1 ± 3.0 ^a
ROS index						
MDA (nmol/mL)	18.3 ± 8.2	17.6 ± 6.2 ^c	17.9 ± 6.4	15.2 ± 4.4 ^c	10.5 ± 5.1	7.6 ± 4.8
NO (μmol/L)	69.5 ± 16.1	61.3 ± 10.0 ^c	70.3 ± 13.4	49.2 ± 7.5 ^c	33.8 ± 17.8	25.5 ± 12.4
SOD (U/mL)	162.4 ± 44.6	259.3 ± 85.7 ^e	266.0 ± 53.0	305.0 ± 58.7	276.7 ± 83.3	281.5 ± 83.7
Zn ²⁺ (μg/mL)	57.6 ± 9.2	84.8 ± 14.2 ^g	69.6 ± 10.5	92.4 ± 12.6 ^g	80.2 ± 8.6	110.8 ± 14.8
Group II (n)	15		16		16	
Rate of efficacy (%)	71.4		62.5		73.9	
Age, y (mean)	35.5		36.5		35.6	
Duration of disease (mos)	21.2		25.3		29.7	
NIH-CPSI	23.9 ± 4.7	13.6 ± 5.8 ^b	20.0 ± 3.9	11.4 ± 2.6 ^a	21.1 ± 3.5	12.0 ± 2.6 ^b
ROS index						
MDA (nmol/mL)	20.9 ± 10.4	12.8 ± 1.6 ^d	16.8 ± 5.4	10.2 ± 3.2 ^d	9.8 ± 4.2	5.7 ± 2.7
NO (μmol/L)	56.0 ± 20.4	48.3 ± 8.6 ^d	72.8 ± 13.0	41.3 ± 11.8 ^d	35.9 ± 15.9	21.2 ± 9.2
SOD (U/mL)	229.3 ± 86.4	379.7 ± 75.4 ^f	200.8 ± 68.7	316.0 ± 66.6	272.3 ± 76.8	286.8 ± 64.2
Zn ²⁺ (μg/mL)	60.3 ± 9.4	109.8 ± 31.7 ^h	80.1 ± 10.6	127.5 ± 26.4 ^h	80.6 ± 10.7	134.8 ± 22.3
Group III (n)	23		23		20	
Rate of efficacy (%)	81.3		75		85	
Age, y (mean)	35.9		34.7		39.3	
Duration of disease (mos)	18.7		20.9		25.7	
NIH-CPSI	24.0 ± 4.1	11.7 ± 3.3	22.4 ± 3.7	9.0 ± 2.2	21.7 ± 3.4	10.6 ± 3.2 ^b
ROS index						
MDA (nmol/mL)	14.5 ± 6.2	14.3 ± 3.9 ^d	17.8 ± 6.7	8.1 ± 3.7 ^d	10.2 ± 3.7	5.5 ± 2.6
NO (μmol/L)	74.9 ± 26.9	53.7 ± 34.4 ^d	62.0 ± 13.8	30.3 ± 9.5 ^d	36.9 ± 16.5	17.7 ± 6.7
SOD (U/mL)	196.6 ± 76.6	427.0 ± 127.5 ^f	211.1 ± 53.3	295.6 ± 30.6	284.8 ± 82.7	272.0 ± 55.0
Zn ²⁺ (μg/mL)	65.2 ± 10.2	115.0 ± 22.1 ^h	80.2 ± 8.7	128.3 ± 18.3 ^h	84.3 ± 14.6	137.5 ± 23.8

Different alphabetic superscripts (a and b, c and d, e and f, g and h) indicate significant differences between groups ($P < .05$).

ROS, reactive oxygen species; Zn, zinc; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; NIH-CPSI, National Institutes of Health - Chronic Prostatitis Symptom Index; MDA, malondialdehyde; NO, nitrogen monoxide; SOD, superoxide dismutase.

analysis was used to analyze the correlation of multiple variables. A P value $< .05$ was selected as a criterion for a statistically significant difference.

(type II $n = 15$, type IIIa $n = 16$, and type IIIb $n = 16$); (3) group III CP patients (type II $n = 23$, type IIIa $n = 23$, and type IIIb $n = 20$).

RESULTS

Baseline Characteristics

Baseline demographic characteristics and clinical parameters are listed in Table 1. The CP patients of every group fell into 3 categories based on the NIH classification of prostatitis⁵: (1) group I CP patients (type II $n = 16$, type IIIa $n = 14$, type IIIb $n = 16$); (2) group II CP patients

The Efficacy Analysis and the Change of NIH-CPSI

Using the preplanned efficacy analysis procedure, the responders rate of type II, type IIIa, and type IIIb were shown in Table 1 in every treatment group, respectively (Table 1). After 6 weeks of treatment, compared with group I, the mean NIH-CPSI total score decreased from 20.0 to 11.4 in patients with type IIIa CP in group II. The

Table 2. The pain, micturition, and QoL domains of the NIH-CPSI score in pre- and posttreatment (mean ± SD)

Categories	Pain Domain		Micturition Domain		QoL Domain	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Group I	8.5 ± 2.9	6.0 ± 2.5 ^a	2.7 ± 2.7	1.0 ± 1.3 ^a	9.5 ± 2.2	7.9 ± 2.7 ^a
Group II	9.3 ± 3.0	4.5 ± 2.1 ^b	3.0 ± 3.1	1.4 ± 1.8 ^a	9.2 ± 1.9	6.5 ± 1.8 ^b
Group III	9.5 ± 2.7	4.2 ± 1.9 ^b	4.0 ± 2.8	0.8 ± 1.1 ^b	9.1 ± 1.8	5.4 ± 1.5 ^b

Different alphabetic superscripts (a and b) indicate significant differences between groups ($P < .05$).

QoL, quality of life.

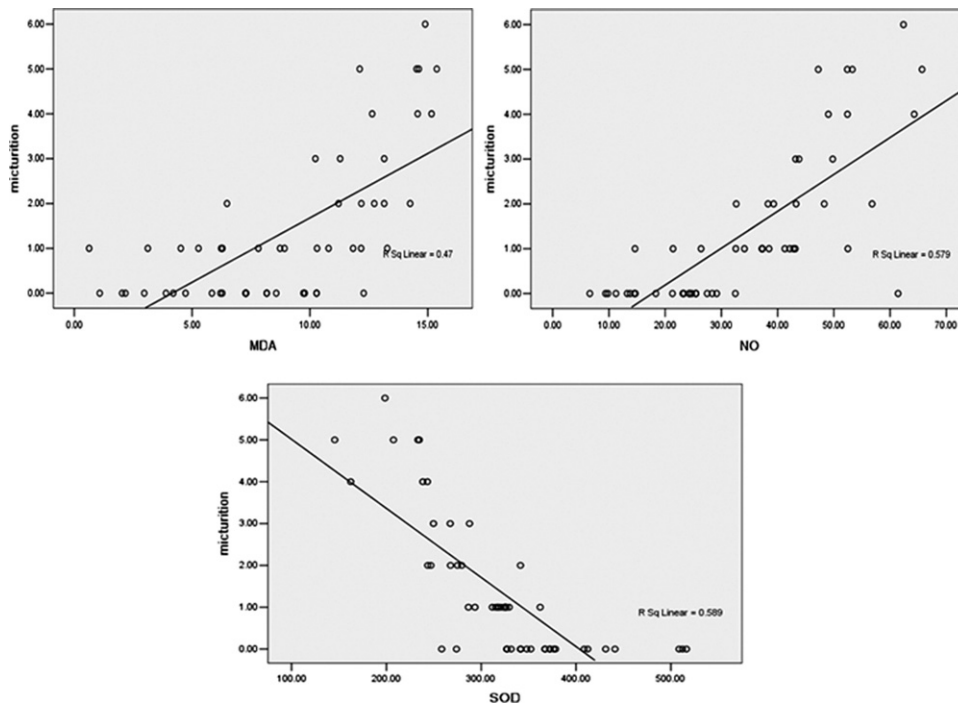


Figure 1. Correlation of MDA, NO, and SOD levels in semen with NIH-CPSI scores (micturition scores).

higher improvement in patients with type IIIa CP compared with the type II and IIIb patients was statistically significant ($P < .01$). There were significant differences between group II or group III and group I ($P < .05$) and no significant difference between group II and group III ($P > .05$) in patients with type IIIb CP (Table 1). The pain domain of the NIH-CPSI also improved among the 3 groups. A higher improvement in group II and group III compared with group I was statistically significant ($P < .01$), whereas there was no statistical significance between group II and group III ($P > .05$). The mean micturition domain of the NIH-CPSI decreased from 4.0 to 0.8 in group III, from 2.7 to 1.0 in group I, and from 3.0 to 1.4 in group II. The baseline-adjusted improvement was significantly higher in group III compared with the other 2 groups ($P < .05$). The mean QoL domain of the NIH-CPSI decreased from 9.2 to 6.5 in group II, from 9.1 to 5.4 in group III, and from 9.5 to 7.9 in group I. A higher improvement in both group II and group III compared with group I was statistically significant ($P < .01$) (Table 2).

The Levels of MDA, SOD, and NO in Semen

Compared with pretreatment, there were obvious decreases of MDA and NO in type II and IIIa patients of group II and group III compared with group I ($P < .01$). There were no obvious changes in MDA and NO in type IIIb patients among the 3 groups ($P > .05$) (Table 1). There was an obvious increase in type II patients, and there were no obvious changes of SOD in type IIIa patients between group II or group III and group I ($P > .05$). There was no significant difference in levels of SOD in type IIIb patients among the 3 groups ($P > .05$) (Table 1).

Zn Levels in Semen

After treatment, there were also obvious increases in type II and IIIa in group II and group III patients compared with group I ($P < .01$), whereas there were no obvious changes of Zn in types II and IIIa patients between group II and group III ($P > .05$) (Table 1).

The Partial Correlation Analysis

The partial correlation analysis showed that there was a significant negative correlation between SOD and micturition ($r = -.510$, $P < .05$), and there was no significant correlation between MDA or NO and micturition ($P > .05$) (Fig. 1).

COMMENT

Currently, CP or CPPS tends to be regarded as a group of syndromes caused by multiple factors, rather than a simple syndrome. Antibiotic treatment is the standard treatment for chronic bacterial prostatitis.¹² Treatment of bacterial prostatitis is hampered by lack of an active antibiotic transport mechanism and the relatively poor penetration of most antibiotics into infected prostate tissue and fluids. Most antibiotics are either weak acids or bases that ionize in biological fluids, which inhibits their crossing the prostatic epithelium,¹³ so their therapeutic efficacy is still unsatisfactory. In addition, it is unclear for the pathogenesis of CPPS, so there is also no standard treatment of CPPS. A variety of other treatment options are reported, such as antibiotics, antiinflammatory agents, and phytotherapeutics. All treatment modalities, however, showed rather limited effects on the symptoms experienced in CPPS. Given the lack of proven efficacy of

conventional therapies, alternative treatment options are urgently needed.

Although several trials have been published evaluating transrectal hyperthermia for the treatment of CP and prostatodynia, this treatment has not gained wide acceptance within the urological community.^{14,15} With the initial limited success of transrectal hyperthermia and thermotherapy, the focus changed to transurethral thermotherapy. Transurethral thermotherapy allows for higher target temperatures and more precise heat delivery. However, the current studies reported that the patients initially treated with transurethral heat therapy had a significant improvement in QoL and symptom severity index, but some patients complained of adverse effects, which included dysuria, hematuria, hematospermia, impotence, premature ejaculation, urinary tract infection, and pain.^{16,17} However, transrectal hyperthermia may be a promising treatment for CP because few side effects have been reported. Therefore, it was concluded that transrectal hyperthermia or thermotherapy for CP needs to be reevaluated because of inconsistencies in outcome measures, modalities of treatment, and study design.

We have presented efficacy comparable with that reported in previous studies using transurethral microwave therapy. It appears to be superior to that of other minimally invasive therapy (transrectal hyperthermia or transurethral needle ablation)^{14,16} or drug treatments¹⁸ used for patients with intractable CP/CPPS. In our series, after 6 weeks of transrectal hyperthermia treatment, the results showed that the efficacy of TRFH was significantly superior to the drug treatments, especially in type IIIa, and the efficacy of the TRFH combined with the antibiotic and α -blockers group was the best among the 3 treatments, suggesting that between radiofrequency, hyperthermia and drugs can produce additive effects.

No adverse events occurred in this study, and the treatments were well tolerated by all groups. This may be mainly because we used transrectal hyperthermia with lower temperatures generated in the prostatic tissue for CP rather than transurethral hyperthermia.

Zhou et al¹⁹ found that chronic bacterial prostatitis likely induces increased nitric oxide and MDA, and decreased SOD. Shahed et al²⁰ demonstrated that gram-positive bacteria in some men with CPPS may be pathogens and these bacteria may be markers of other inflammatory or autoimmune mechanisms, leading to oxidative stress and CPPS. In the present study we found that the levels of MDA and NO were decreased, whereas SOD was increased significantly in the posttreatment of CP than those in the pretreatment. Interestingly, there was a significantly better improvement for group II compared with group I in types II and IIIa patients; and there was a significant negative correlation between SOD and the NIH-CPSI micturition score. The mechanism of TRFH may be that it accelerates the resolution of the inflammatory process, recovery of hemodynamics in the

prostate, and structure and function of cell membranes in prostatic secretion.

Zn has been known to be associated with the prostate gland for many years. It has been identified in a number of species of animals, notably the rat, monkey, and human. In the past, a number of investigators have shown that patients with bacterial prostatitis have consistently lower Zn concentrations, in prostatic fluid than normal. Patients with nonbacterial prostatitis had lower Zn concentrations, but this could be corrected by administering oral Zn.²¹ Cho et al⁶ found that high levels of prostatic Zn were associated with prostatic antimicrobial activities and were decreased in patients with chronic prostatitis. In the present study, we also showed that Zn levels were much higher in the type II and type IIIa patients than in the type IIIb patients after treatment. Furthermore, the effect of transrectal radiofrequency hyperthermia with antibiotics and α -blockers was superior to drugs alone. It was concluded that radiofrequency hyperthermia changes the local prostatic microenvironment to facilitate penetration of antibiotics into infected prostate tissue and fluids, and, finally, Zn also penetrated into prostate fluids.

We found that the pain domain of the NIH-CPSI also improved among the 3 groups. The pain domain of the NIH-CPSI decreased from 9.5 to 4.2 after the radiofrequency hyperthermia treatment, which alters the sensory nerves in the prostatic stroma that convey pain sensations and α -adrenergic regulations.²²

Although 6 weeks of transrectal radiofrequency hyperthermia appears to benefit many men diagnosed with chronic prostatitis, long-term efficacy should be evaluated. In addition, the duration of transrectal radiofrequency hyperthermia should be further explored.

CONCLUSIONS

Our study reveals TRFH as an effective therapy option for CP, especially type IIIa or type IIIb CP. The results of the TRFH with tamsulosin plus clarithromycin group were superior to the TRFH group or the tamsulosin plus clarithromycin group alone. Compared with pretreatment, differences in ROS levels and Zn in CP patients suggest that these factors could be used as a biomarker to evaluate the symptoms of CP and the effects of treatment.

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