Efficacy of Antioxidant Treatment on the Symptoms of Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome Category IIIA

Kronik Prostatit Kategori Tip IIIA / Kronik Pelvik Ağrı Sendromlu Hastalarda Antioksidan Tedavinin Semptomlar Üzerine Etkisi

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of antioxidant treatment on the symptoms in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) category IIIA.

Material and Methods: We retrospectively evaluated the data of patients with chronic prostatitis/chronic pelvic pain syndrome category IIIA who were treated by Progeny- M®, an antioxidant agent, between October 2016 and December 2017. The pretreatment and posttreatment symptoms were assessed using the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI). A reduction of the NIH-CPSI total score by ≥25% after the treatment was accepted as an improvement. A value of $P < 0.05$ was considered statistically significant.

Results: Thirty-five out of 53 patients diagnosed with chronic prostatitis were CP/CPPS category IIIA. Seventeen of them were treated with antioxidant agent (Progeny- M®) for a month. Mean NIH-CPSI total score was significantly decreased after the treatment with Progeny-M® compared to the pretreatment mean score ($p < 0.001$). Pretreatment mean pain, urinary and quality of life scores of NIH- CPSI (12.1±3.8, 4.7±2.8, 7.6±2.7, respectively) were significantly decreased compared to posttreatment scores (8.2±4.2, 3.1±2.0, 5.2±2.6) ($p < 0.001$, $p=0.002$, $p=0.004$, respectively).

Conclusion: The mean total, pain, urinary and quality of life NIH-CPSI scores significantly decreased after 4 weeks of Progeny-M® treatment in patients with CP/CPPS category IIIA. 58.8% the patients had improved NIH-CSPI scores after the treatment.

Key Words: Chronic prostatitis, Chronic pelvic pain syndrome, Antioxidant therapy, Chronic prostatitis symptom index

ÖZ

Amaç: Çalışmanın amacı kronik prostatit kategori tip IIIA / kronik pelvik ağrı sendromlu (KP/KPAS) hastalarda antioksidan tedavinin semptomlar üzerine etkisinin değerlendirilmesidir.

Gereç ve Yöntemler: Ekim 2016 ile Aralık 2017 arasında antioksidan ajan olan Progeny-M® ile tedavi edilen KP/KPAS kategori IIIA hastaların verileri retrospektif olarak değerlendirildi. Tedavi öncesi ve tedavi sonrası semptomların değerlendirilmesinde National Institute of Health- Kronik Prostatit Semptom İndeksi (NIH-KPSİ) kullanıldı. Tedaviden sonra NIH-KPSİ toplam skorunda %25'ten fazla azalma tedaviye yanıt olarak kabul edildi. $P < 0.05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Kronik prostatit tanısı konan 53 hastanın 35'i KP/KPAS kategori IIIA idi. Bunlardan 17'si bir ay boyunca bir antioksidan ajan olan Progeny-M® ile tedavi edilmiş hastalardı. Progeny-M® ile tedavi sonrası ortalama toplam NIH-KPSİ skoru, tedavi öncesi ortalama skorla karşılaştırıldığında anlamlı olarak azaldı ($p < 0,001$). Tedavi öncesi ortalama ağrı, üriner belirti ve yaşam kalitesi skorları (sırasıyla 12,1±3,8, 4,7±2,8, 7,6±2,7), tedavi sonrası skorlara göre (8,2±4,2, 3,1±2,0, 5,2±2,6) anlamlı derecede azaldı ($p < 0,001$, $p = 0,002$, $p = 0,004$).

Sonuç: KP/KPAS kategori IIIA olan hastalarda 4 hafta Progeny-M® tedavisinden sonra ortalama toplam ağrı, üriner semptom ve yaşam kalitesi NIH-KPSİ skorları anlamlı olarak azaldı. Hastaların % 58,8 'inde NIH-CSPI skorunda tedaviden sonra iyileşme görüldü.

Anahtar Sözcükler: Kronik prostatit, Kronik pelvik ağrı sendromu, Antioksidan tedavi, Kronik prostatit semptom indeksi

INTRODUCTION

Prostatitis is a very common urologic disease. The prevalence of prostatitis-like symptoms ranges from 2% to 9.7% (1). In 1999, the National Institutes of Health (NIH) proposed a new classification of prostatitis defined according to the assessment of clinical presentation by the presence or absence of white blood cells (WBCs) in the semen, in expressed prostatic secretion (EPS), or in the first voided urine (VB3) after prostatic massage, and by the presence or absence of traditional uropathogens detected by traditional culture techniques (2,3).

In the NIH classification, category III is a chronic non-bacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) characterized by discomfort or pain in the pelvic region for more than 3 months within the past 6 months with variable urinary symptoms, sexual dysfunction and no demonstrable infection. There are two distinct forms in category III; IIIA inflammatory CP/CPPS with WBCs in semen, EPS, or VB3, and IIIB non-inflammatory CP/CPPS without WBCs in semen, EPS, or VB3. CP/CPPS is a common clinical syndrome occurring in 15% of men and it makes up 90–95% of all prostatitis cases (4,5). The National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) is a reliable tool for assess the severity of symptoms, quality of life (QoL) score and impact of CP/ CPPS (6). NIH-CPSI provides an objective outcome measure for treatment response in research studies.

The etiology of CP/CPPS is still unclear although many studies suggests a possible role of infectious, inflammatory, immunologic and neuronal causes (7). The etiology of CP/CPPS is still unclear and the underlying pathophysiological mechanisms of the CP/CPPS is poorly understood. For these reasons, there is no standard treatment for the CP/CPPS and most of the time treatment results are frustrating for both patients and urologists.

Treatment options are antibiotics, alpha-blockers, non-steroid anti-inflammatory drugs (NSAID) and phytotherapeutic agents in men with chronic pelvic pain syndrome (8-11). Several studies showed that seminal oxidative stress (OS) could be an etiologic factor in bacterial prostatitis and CP/CPPS (12,13). If excessive reactive oxygen species (ROS) production or imbalance occurs between ROS production and total antioxidant capacity (TAC), it leads to oxidative stress. ROS overproduction/decreased antioxidants have been shown in semen of CP/CPPS patients in these studies. These studies suggest that antioxidant therapy could be an alternative option in the treatment of CP/CPPS patients.

The aim of this retrospective study was to evaluate symptom improvements treated by antioxidant agent (Progeny- M®) in CP/CPPS category IIIA patients. Treatment response was evaluated by the validated Turkish version of NIH-Chronic Prostatitis Symptom Index.

MATERIAL and METHODS

We retrospectively reviewed our recorded data of chronic prostatitis patients attending our outpatient clinic between October 2016 and December 2017. The following evaluations were our routine evaluation of all prostatitis patients: detailed history, physical examination including digital rectal examination of the prostate (DRE), urine analysis and midstream urine culture and serum total PSA level was measured on the first visit if patient age is 45 or over. If there was no infection in urine culture, our further evaluation was prostatic massage and 2-cup test including microscopic examination and culture of EPS and VB3 for the WBC count after 4-5 days sexual abstinence. If there was a suspicion of symptoms of urethritis or history of unprotected intercourse, samples from the urethra were taken for the culture of *Chlamydia trachomatis, Ureaplasma urealyticum,* and *Mycoplasma hominis*. Patients with prostatitis-like symptoms for more that 3 months within the past 6 months, negative urine/EPS/urethral cultures, 10 or more WBC on microscopic examination in EPS or VB3 on 2-cup test were diagnosed as CP/ CPPS category IIIA. If there was less then 10 WBC in EPS, patients were diagnosed as CP/ CPPS IIIB. All patients completed the validated Turkish version of NIH-Chronic Prostatitis Symptom Index form when the CP/CPPS diagnosis was made and after 1 month with any medical treatment. We selected CP/ CPPS category IIIA patients who were treated with antioxidant agent Progeny-M® for one month (one capsule q8h) from our recorded data. Patients who had a history of previous medication for the treatment of prostatitis in the last 3 months were excluded from the study.

Ingredients of Progeny-M® are presented in Table I. Pretreatment and posttreatment mean NIH-CPSI total and domain scores were compared to evaluate symptom improvements in patients with CP/CPPS category IIIA. A reduction of more than 25% of the NIH-CPSI total score was considered an improvement (14).

Statistical Analysis

The statistics are presented as mean ± standard deviation (SD). The paired t-test was used for statistical analysis. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Our recorded data revealed that a total of 53 patients were diagnosed with CP/CPPS between October 2016 and December 2017. Thirty-five of them were diagnosed as CP/CPPS category IIIA. 17 out of 35 patients were treated with antioxidant agent (Progeny-M, dosage of 3 capsules/day) for a month. Our recorded data revealed that there

were no serious side-effects of Progeny-M® therapy and all patients (17/17,100%) completed four weeks of therapy. One patient reported increased sexual drive and another had complaint of weight gain. Patient characteristics are presented in Table II.

The mean age of the patients was 40.7 ± 11.0. Pretreatment and post treatment mean total NIH-CPSI scores were 24.4 ± 6.2 and 16.6 ± 7.3, respectively. Mean NIH-CPSI total score was significantly decreased (-31.9 %) after the treatment with Progeny-M® compared to pretreatment mean score ($p < 0.001$ paired- t test). Pretreatment mean pain, urinary and quality of life scores of NIH- CPSI were significantly decreased compared to posttreatment scores (Table III). Total 10 out of 17 (58.8%) patients treated with Progeny-M had improvement in both the total NIH-CSPI score and QoL score after 4 weeks.

Table I: Ingredients in each capsule of Progeny-M®.

L-carnitine	168 mg
L-Arginine	138.3 mg
Vitamin C	67 mg
Vitamin E	42 mg
Pine bark extract	33.4 mg
Coenzyme Q10	30 mg
L-cysteine	26.7 mg
Zinc	13.3 mg
Beta-carotene	1.0 mg
Folic acid	267 µg
Selenium	20 µg
Vitamin D	3.3 µg

DISCUSSION

In the present study, we retrospectively analyzed our recorded data of patients with CP/CPPS category IIIA who were treated with the antioxidant agent Progeny-M® for a month. We found that mean total, pain, urinary and quality of life NIH-CPSI scores significantly decreased after 4 weeks of Progeny-M® treatment in patients with CP/CPPS category IIIA. 58.8% of the patients had improvement in their NIH-CSPI scores (a reduction of the NIH-CPSI total score by ≥25%) after the treatment. Our results showed that treatment with the antioxidant agent Progeny-M® reduced CP/CPPS- related symptoms as shown by decreased NIH-CPSI scores.

Studies suggest that seminal oxidative stress could be an etiologic factor in patients with CP/CPPS (13,15). Pasqualotto et al. showed that increased seminal reactive oxygen species and decreased total antioxidant capacity of patients with CP/CPPS compared to control subjects. Their results suggest that CP/CPPS patients have oxidative stress, irrespective of the leukocytospermia status. Inflammation is the primary pathology in chronic prostatitis and the polymorphonuclear leucocytes the major source of ROS in semen of prostatitis patients. Although there is no identified microorganism in CP/CPPS patients, continuous inflammatory response and ROS production due to previous infection could be the responsible pathology. Potts et al. emphasized the importance of *Ureaplasma urealyticum* in

Table II: Characteristics of the patients at baseline.

	Age (years) n: 17	PSA (ng/mL) n: 7	Prostate volume (ml) n: 17	NIH-CPSI Scores n: 17
CP/CPPS category IIIA	40.7 ± 11.0	1.4 ± 0.9	19.7 ± 5.7	24.4 ± 6.2

CP/CPPS Chronic non-bacterial prostatitis/chronic pelvic pain syndrome
NIH-CPSI National Institutes of Health Chronic Prostatitis Symptom Index

Table III: Changes in mean NIH-CPSI scores after 4 weeks of treatment.

NIH-CPSI	Baseline ± sd	After 4 weeks ± sd,	p value
Pain	12.1± 3.8	8.2 ± 4.2, (-32.2)	$p < 0.001$
Urinary	4.7± 2.8	3.1± 2.0 , (-34)	p=0.002
Quality of Life	7.6± 2.7	5.2 ± 2.6, (-31)	p=0.004
Total	24.4± 6.2	16.6 ± 7.3 (-31.9)	$p < 0.001$

In parentheses is the decrease percentage of the NIH-CPSI score after treatment.
NIH-CPSI National Institutes of Health Chronic Prostatitis Symptom Index

patients with CP/CPPS (16). Since the semen or prostatic fluid culture of these microorganisms are not routine in the evaluation of chronic prostatitis patients, it is possible to incorrectly categorize chronic bacterial prostatitis as CP/CPPS. For avoiding this, we took urethral samples from our patients if there was urethritis symptoms or a history of suspicious sexual intercourse existed.

The significant improvement in symptoms of our CP/CPPS category IIIA patient group could be related to the antioxidant ingredients of Progeny-M®. Since the other studies showed the importance of oxidative stress in the etiology of CP/CPPS patients, antioxidant treatment using several agents could be an appropriate option for this group of patients.

Several studies have been shown that treatment with antioxidant agents could improve patient symptoms in CP/CPPS. Morgia et al reported efficacy of *Serenoa repens,* selenium and lycopene combined therapy in patients with CP/CPPS category IIIA (17). They showed a significant improvement in mean CPSI total score (-51.6%) in the combined treatment group and (-26.06%) in the *Serenoa repens* treatment only group.

Another agent, Quercetin, is plant-derived bioflavonoid and has been used for the treatment of CP/CPPS patients. Quercetin has antioxidant and anti-inflammatory properties. Shoskes et al studied the effect of Quercetin in NIH-CPSI scores in patients with CP/CPPS (18). They found that patients taking Quercetin had reduction in mean NIH-CPSI scores from 21.0 to 13.1 in their double-blind, placebo-controlled study.

Oka et al reported the effect of the phytotherapeutic agent Eviprostat on non-bacterial prostatitis in the rat model (19). Eviprostat has antioxidant and anti-inflammatory properties. They found that Eviprostat treatment significantly suppressed oxidative stress and proinflammatory cytokines in the inflamed prostate in a rat model of nonbacterial prostatitis. They suggested Eviprostat could be useful in the treatment of CP/CPPS patients via its suppressing effect on oxidative stress.

Hajighorbani et al showed a protective effect of pentoxifylline on carrageenan-induced chronic non-bacterial prostatitis in rats (20). They proposed that pentoxifylline's protective effect was via its anti-oxidant property evidenced by decreased serum malondiadehyde (MDA) levels in the rat chronic non-bacterial prostatitis model.

In the light of the above-mentioned studies, oxidative stress could be a significant factor in the pathophysiology of the CP/CPPS and antioxidant therapy could be a promising alternative in the future. We found that 4 weeks of Progeny-M® treatment significantly decreased the complaints of patients with CP/CPPS category IIIA. There are several drawbacks of our study which are the retrospective design and the fact it was not randomized or placebo-controlled. The present study has promising data for further investigations on the importance of oxidative stress and efficacy of antioxidant treatments in patients with CP/CPPS category IIIA. Treatment response could also be evaluated with seminal plasma ROS and antioxidant enzyme levels in addition to the NIH-CPSI score evaluation in future projects.

CONCLUSIONS

We found that mean total, pain, urinary and quality of life NIH-CPSI scores significantly decreased after 4 weeks of Progeny-M® treatment in patients with CP/CPPS category IIIA. 58.8% patients had improvement in the NIH-CSPI scores after the treatment. Further randomized and placebo-controlled studies are needed to evaluate the efficacy of antioxidant treatments in patients with CP/CPPS category IIIA.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Krieger JN, Lee SW, Jeon J, Cheah PY, Liong ML, Riley DE. Epidemiology of prostatitis. Int J Antimicrob Agents 2008; 31 Suppl. 1: 85-90.
2. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999; 282:236-7.
3. Nickel JC: Prostatitis syndromes: An update for urologic practice. Can J Urol 2000;7: 1091-8.
4. Schaeffer AJ, Datta NS, Fowler JE Jr, Krieger JN, Litwin MS, Nadler RB. Chronic Prostatitis Collaborative Research N. 2002 Overview summary statement. Diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Urology 2002; 60:1-4.
5. Schaeffer AJ, Knauss JS, Landis JR, Propert KJ, Alexander RB, Litwin MS, Nyberg LM. Leukocyte and bacterial counts do not correlate with severity of symptoms in men with chronic prostatitis: The National Institutes of Health Chronic Prostatitis Cohort Study. Journal of Urology 2002; 168:1048-53.

6. Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhoun EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institutes of Health chronic prostatitis symptom index: Development and validation of a new outcome measure. J Urology 1999; 162:369-75.
7. Breser ML, Salazar FC, Rivero VE, Motrich RD. Immunological mechanisms underlying chronic pelvic pain and prostate in chronic pelvic pain syndrome. Front Immunol 2017; 8:898.
8. Nickel JC, Downey J, Clark J, Casey RW, Pommerville PJ, Barkin J, Steinhoff G, Brock G, Patrick AB, Flax S, Goldfarb B, Palmer BW, Zadra J. Levofloxacin for chronic prostatitis/chronic pelvic pain syndrome in men: A randomized placebo-controlled multicenter trial. Urology 2003;62(4):614-7.
9. Nickel JC, Narayan P, McKay J, Doyle C. Treatment of chronic prostatitis/ chronic pelvic pain syndrome with tamsulosin: A randomized double blind trial. J Urol 2004;171(4):1594-7.
10. Zhao WP, Zhang ZG, Li XD, Yu D, Rui XF, Li GH, Ding GQ. Celecoxib reduces symptoms in men with difficult chronic pelvic pain syndrome (Category IIIA). Braz J Med Biol Res 2009;42(10):963-7.
11. Rugendorff EW, Weidner W, Ebeling L, Buck AC. Results of treatment with pollen extract (cernilton N) in chronic prostatitis and prostatodynia. Br J Urol 1993;71: 433-8.
12. Shahed AR, Shoskes DA. Oxidative stress in prostatic fluid of patients with chronic pelvic pain syndrome: correlation with gram positive bacterial growth and treatment response. J Androl 2000;21:669-75.
13. Pasqualotto FF, Sharma RK, Potts JM, Nelson DR, Thomas AJ, Agarwal A. Seminal oxidative stress in patients with chronic prostatitis. Urology 2000;55(6):881-5.
14. Cai T, Verze P, La Rocca R, Palmieri A, Tiscione D, Luciani LG, Mazzoli S, Mirone V, Malossini G. The Clinical Efficacy of Pollen Extract and Vitamins on chronic prostatitis/chronic pelvic pain syndrome is linked to a decrease in the pro-inflammatory cytokine interleukin-8. World J Mens Health 2017; 35(2):120-8.
15. Potts JM, Pasqualotto FF. Seminal oxidative stress in patients with chronic prostatitis. Andrologia 2003; 35:304-8.
16. Potts JM, Sharma RK, Pasqualotto FF, Nelson DR, Agarwal A. Association of *Ureaplasma urealyticum* infection with abnormal seminal reactive oxygen species and absence of leukocytospermia. J Urol 2000;163:1775-8.
17. Morgia G, Mucciardi G, Galì A, Madonia M, Marchese F, Di Benedetto A, Romano G, Bonvissuto G, Castelli T, Macchione L, Magno C. Treatment of chronic prostatitis/ chronic pelvic pain syndrome category IIIA with Serenoa repens plus selenium and lycopene (Profluss) versus S. repens alone: An Italian randomized multicenter-controlled study. Urol Int 2010; 84:400-6.
18. Shoskes DA, Zeitlin SI, Shahed A, Rajfer J. Quercetin in men with category III chronic prostatitis: A preliminary prospective, double-blind, placebo-controlled trial. Urology 1999;54(6): 960-3.
19. Oka M, Ueda M, Oyama T, Kyotani J, Tanaka, M. Effect of the phytotherapeutic agent Eviprostat on 17beta-estradiol-induced nonbacterial inflammation in the rat prostate. Prostate 2009;69:1404-10.
20. Hajighorbani M, Ahmadi-Hamedani M, Shahab E, Hayati F, Kafshdoozan K, Keramati K, Amini AH. Evaluation of the protective effect of pentoxifylline on carrageenan-induced chronic non-bacterial prostatitis in rats. Inflammopharmacology 2017;25(3):343-50.