

# The Efficacy of Zinc for Treatment of Chronic Prostatitis

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## ABSTRAK

**Tujuan:** untuk meneliti efektivitas suplementasi seng pada pengobatan prostatitis kronik. **Metode:** penelitian ini merupakan uji klinis teracak yang dilaksanakan pada 120 pasien prostatitis kronik (NIH IIIA) berdasarkan evaluasi awal dan penyingkiran kemungkinan diagnosis lain. Kelompok yang diteliti mendapatkan suplementasi seng sulfat oral sebanyak 220 mg setiap hari dalam bentuk kapsul tanpa disertai suplemen lainnya. Kelompok kontrol mendapatkan plasebo. Skor NIH-CPSI pasien diperiksa setiap 4 minggu selama 12 minggu. **Hasil:** sebanyak 101 pasien mengikuti penelitian sampai selesai. Tidak ada perbedaan bermakna secara statistik dalam skor dan sub-skor NIH-CPSI antar kedua kelompok sebelum intervensi dilakukan. Penurunan skor dan sub-skor tampak lebih nyata pada kelompok perlakuan setelah penelitian dimulai; meski perbedaan tersebut tidak berbeda bermakna secara statistik. Selanjutnya, perbedaan skor total dan skor nyeri setelah 12 minggu pengamatan, ternyata bermakna secara statistik ( $p=0,003$  dan  $p=0,02$ ). **Kesimpulan:** suplementasi seng (Zn) bermanfaat dalam penanganan pasien dengan prostatitis kronik NIH-III A. Hal ini dapat disebabkan oleh sifat antibakteri dan peran imunomodulator seng organik di dalam tubuh.

**Kata kunci:** prostatitis, seng, gejala berkemih iritatif, gejala obstruktif, plasebo.

## ABSTRACT

**Aim:** to investigate the efficacy of zinc supplementation in chronic prostatitis treatment. **Methods:** present randomized clinical trial was conducted on 120 patients with diagnosis of chronic prostatitis (IIIA NIH) after preliminary evaluation and ruling out other conditions. The study group received oral zinc sulfate 220 mg daily as capsule without any other supplements. The control group received placebo. Subjects were examined for NIH-CPSI scores every 4 weeks for 12 weeks. **Results:** 101 subjects completed the study. There were no statistically significant differences in scores and sub-scores of NIH-CPSI between groups before intervention. Decline in the score and sub-scores were more prominent in case group after beginning of the study; though the differences were not statistically significant. Furthermore, the differences in total score and pain score at 12 weeks follow was statistically significant ( $p=0.003$  and  $p=0.02$ , respectively). **Conclusion:** zinc supplements may benefit in management of patients with chronic prostatitis NIH-III A. It can be attributable to anti-bacterial and immuno-modulatory functions of organic zinc in the body.

**Key words:** prostatitis, zinc, irritative urinary symptoms, obstructive symptoms, placebo.

## INTRODUCTION

Prostatitis is a common condition, with an estimated prevalence of about 10% in United States.<sup>1</sup> Prostatitis-like symptoms is relatively common in adult men, with an estimated prevalence in North America ranging from 2.2% to 9.7%. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) comprises 90-95% of cases.<sup>2</sup> The National Ambulatory Care Surveys from 1990 to 1994 has reported that prostatitis was coded as the diagnosis in 8% of urologist office visits and in 1% of primary care physician visits, translating into 2 million office visits annually in USA. The incidence of acute prostatitis or prostatitis not otherwise specified increases dramatically from the second to the third decade.<sup>2</sup> It is a frequently occurring disease with a complex and heterogeneous etiology.<sup>2,3</sup> The incidence of explicit diagnosis of chronic prostatitis (CP) increases with age, most dramatically in men 55 years of age.<sup>4,5</sup>

Chronic Prostatitis Symptom Index (NIH-CPSI) total score and pain and quality of life sub-scores are sensitive to clinically important improvements within individual patients over time.<sup>6-9</sup>

Zinc is essential for growth and development. At the cellular level, it is critically involved in proliferation, differentiation, and apoptosis.<sup>10</sup> Zinc has diverse biological functions in enzymatic catalysis, redox regulation, cellular signal transduction, the immune system, and neurons.<sup>11,12</sup> Zinc ion inhibits the prolyl-hydroxylation process and consequently stabilizes Hypoxia-inducible factor 1 (HIF-1), which facilitates the expression of survivin that promotes cell survival and proliferation.<sup>13</sup> It is confirmed that oxidative stress is also present in cases of chronic prostatitis.<sup>14</sup> Zinc has played a part in few recent studies as an alternative treatment for chronic prostatitis. In 2004, in a study in China, using Zinc simultaneously with antibiotics lowered the severity of NIH-CPSI symptoms (pain, urine-related symptoms and quality of life) and reduced the maximum intra-urethral pressure in contrast to the group which was treated only with antibiotics.<sup>16</sup> Another study demonstrated that injection of Zinc inside the prostate of mice with prostatitis, promoted

an inhibiting effect on the growth of bacteria in proportion to the control group.<sup>17</sup>

With respect to the studies on zinc and its effect on prostatitis, this study aimed to evaluate efficacy of zinc supplementation for the treatment of CP/CPPS.

## METHODS

Present study was a double blind randomized controlled trial. The participants were selected from patients referred to urology clinic of a university teaching hospital, Arak city, Iran.

The study population consisted of males 18-40 years old with symptoms of discomfort or pain in the pelvic region for at least a 3-month period within the 6 months rightly before baseline screening. Each patient was evaluated at study entry by basic examination, urinalysis and culture, NIH-CPSI score, lower urinary tract testing, serum concentration of PSA antigen, urodynamics, and urine cytology by one of the researchers to rule out other credible conditions.

Patients were excluded from the study if they had received any medication for the disease within last 30 days, had experienced 2 or more urinary tract infections within the previous 12 months, or had medical conditions such as abnormal test results of digital rectal examination (except benign prostate enlargement), prostate specific antigen greater than 10.0 ng/mL, abnormal findings in above measured preliminary evaluation, and liver or renal insufficiency.

Patients selection was continued until 120 individual with diagnosis of chronic prostatitis (IIIA classification according to NIH) were identified and assented to study participation, assuming about 20% withdrawal rate. The final goal was participation of at least 100 patients in the study, as suggested by a biostatistist. The patients were randomly divided into two groups 1:1. Both groups received oral Perazosin 2 mg daily to offer potential treatment for their disease symptoms, as suggested by local ethical committee. Group A (study group) received oral Zinc sulfate 220 mg daily as capsule without any other supplements. The prescribed dose was determined arbitrarily after review of related literatures.<sup>10,11</sup> The drugs were purchased from a pharmacy and had been produced by Al-

Hawi pharmaceutical Co, Tehran, Iran. Group B (control group) received placebo instead of Zinc supplement. The placebo drugs had been produced by Al-Hawi pharmaceutical Co, Tehran, Iran too. The patients took their prescribed drugs from a predetermined pharmacy. The pharmacist was conferring their medications based on the letter C or D alternately which was been written on the drug package. Neither the examining physician nor the pharmacist had not known true constituent of the packages.

The patients were examined for NIH-CPSI scores 18 by the same physician every 4 weeks for 12 weeks. If any patient had nausea, GI complaints, or sensitivity reaction to the drug, they would be excluded from the study and the medication would be changed.

The study was approved by local ethical committee of Arak's University of Medical Sciences. All eligible patients provided informed written consent for participation in the study.

### Statistical Analysis

Data analysis was performed by SPSS software version 15.00 for Windows by using independent sample T-test. Data are presented as mean $\pm$  SD for continues variables and number and percent for categorical variables.

### Sample Size Calculation

Since we could not find any previous study concerning the effects of zinc on chronic prostatitis, we used pooled data from our previous patients afflicted with chronic prostatitis to calculate their mean IPSS score. We used "PS: Power and Sample Size Calculation version 3.0, 2009" software available from <http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize> to calculate the sample size. With a mean IPSS score of  $15 \pm 3$  and considering a difference in IPSS score of 2 as clinically valuable, using independent sample design with  $\alpha = 0.05$  (two-tailed) and power=90% and the ratio of control to experimental patients set as 1, the sample size was calculated as 48 cases in each group.

## RESULTS

Nineteen patients could not complete the treatment course for various reasons, mainly

failed to follow up or had GI complaints. The remaining 100 comprised 48 in case group and 53 in control group. General features of the patients are demonstrated in **Table 1**.

**Table 1.** General features of the study patients in zinc and placebo groups

	Zinc group (n=48)	Placebo group (n=53)	p
Age (mean $\pm$ SD)	28.24 $\pm$ 11.20	27.90 $\pm$ 10.75	0.824
Duration of the disease (months) (mean $\pm$ SD)	13.12 $\pm$ 2.5	12.66 $\pm$ 1.9	1.123
Body Mass Index (mean $\pm$ SD)	22.74 $\pm$ 2.23	23.59 $\pm$ 3.11	0.732

NIH-CPSI score was used to evaluate severity of the symptoms in the patients and their response to the therapy. The scores of the studied patients before the intervention, and 4, 8, and 12 weeks afterward are demonstrated in **Table 2**. As it can be seen, there were no statistically significant differences in scores and sub-scores of NIH-CPSI between groups before intervention. Decline in the score and sub-scores were more prominent in case group after beginning of the study; though the differences were not statistically significant, apart from differences in total score and pain score at 12 weeks after start of the study ( $p=0.003$  and  $p=0.002$ , respectively).

Five subjects in case group and three subjects in control group developed GI complaints in the form of dyspepsia during the study but the difference in the occurrence of these complications was not statistically significant between the two groups. They excluded from the study and their drugs were changed.

## DISCUSSION

Results of present suggest that zinc supplementation may help individuals with chronic prostatitis in reducing or relieving their symptoms. Zinc supplementation reduced significantly total score and pain score after 12 weeks of treatment.

Chronic abacterial prostatitis is a common but enigmatic condition that has been termed "a wastebasket of clinical ignorance".<sup>20</sup> Successful management of chronic prostatitis presents a

**Table 2.** NIH-CPSI score (mean± SD) of the study patients before the treatment, and 4, 8, and 12 weeks afterward

		<b>Total score (0-43)</b>	<b>Pain score (0-21)</b>	<b>Urination score (0-10)</b>	<b>Quality of life score (0-12)</b>
Before the study	Placebo group	23.89±6.38	11.56±2.00	4.33±1.75	8.00±2.63
	Zinc group	24.11±7.38	11.38±2.91	4.52±1.88	8.21±2.59
4 weeks after the study	Placebo group	21.77±5.28	10.72±1.95	3.51±1.34	7.54±1.99
	Zinc group	21.75±5.70	10.41±2.01	3.77±1.38	7.57±2.31
8 weeks after the study	Placebo group	19.77±6.15	10.12±2.17	3.11±1.22	6.54±2.76
	Zinc group	18.85±5.39	9.66±1.75	3.08±1.43	6.11±2.21
12 weeks after the study	Placebo group	18.81±6.22	9.63±2.17	2.85±1.54	6.33±2.51
	Zinc group	16.56±6.68	8.12±2.11	2.66±2.01	5.78±2.56

difficult challenge for physicians and patients because of the lack of effective evidence based, disease specific treatment options.<sup>2</sup> Of the available treatment options for CP/CPPS none has consistently demonstrated efficacy in clinical studies. A common treatment of CP/CPPS is the administration of alpha 1-adrenergic receptor antagonists (alpha -blockers) with proven efficacy in relieving LUTS associated with BPH.<sup>2,9,21</sup>

Accumulating evidence for proinflammatory cytokines in the pathogenesis of CPPS provides a direction for new treatment approaches.<sup>5</sup> Novel therapeutic approaches that block the effects of cytokines appear promising, effective, and safe in the treatment of CPPS patients.<sup>12</sup> Zinc supplements can fall into this kind. Moreover it has been revealed that oxidative stress is an important pathogenesis mechanism in several male genital tract disorders that are frequently diagnosed, namely BPH and different forms of chronic prostatitis (NIH categories IIIA, IIIB, and IV). It is generally accepted that inflammation is accompanied by oxidative stress, and therefore the increased oxidative stress levels in NIH IIIA and NIH IV category prostatitis patients was a presumptive result.<sup>14</sup>

In addition, zinc supplementation is recommended in men with all forms of prostatitis.<sup>8,15</sup> Investigators have found that chronic prostatitis is associated with a decrease in the zinc level. Hence, maintaining the zinc at normal level would be helpful for the CBP treatment.<sup>22</sup>

Wu, et al<sup>22</sup> have evaluated the anti-inflammatory effects of Qian-Yu, a Chinese

herbal product in chronic bacterial prostatitis in animal model. They achieved promising results. They believe that the drug is effective in CBP treatment through increase in prostatic zinc levels.<sup>22</sup> Cho, et al<sup>23</sup> have investigated the inhibition of bacterial growth in the rat prostate with chronic prostatitis after intraprostatic injection of zinc and compared two different types of zinc delivery. They have concluded that the intraprostatic injection of zinc in a chronic bacterial prostatitis rat model inhibits bacterial growth by increasing the prostatic zinc levels without affecting the systemic zinc levels. They suppose zinc may be used to treat chronic prostatitis at the point of its pathogenesis.<sup>23</sup> Deng, et al<sup>24</sup> have studied the efficacy of biological organic zinc in the treatment of chronic bacterial prostatitis. They have suggested that biological organic zinc markedly decreases NIH-CPSI score in patients with CBP compared to antibiotic treatment.<sup>24</sup>

This study results confirmed that zinc supplements may be effective in management of chronic prostatitis NIH- IIIA. It can be attributable to anti-bacterial and immunomodulatory functions of organic zinc in the body. It is consistent with study of Deng, et al.<sup>25</sup>

The prescribed dose of zinc supplement was kept at the minimum (220 mg per day) in current study. The study continued for 3 months. Since chronic prostatitis needs long-term treatment, it is plausible that increase the dosage of zinc supplement and/or duration of the treatment more prominently improve symptoms in the patients. A minority of our patients developed GI side effect of the drug. These cannot be directly connected

to the drug itself; since GI upsets occurred in 3 patients from control group too.

Present study opened a relatively new aspect in the pathogenesis and management of chronic prostatitis. However before definite conclusion, conduction of larger scaled studies, possibly with higher doses and more prolonged treatment courses is recommended to clarify true role of zinc supplementation treatment of patients with chronic prostatitis.

## CONCLUSION

Zinc with a dose of 220 mg daily have benefit to reduce total NIH-CPSI and pain scores in chronic prostatitis patients.

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