

# Comparison of the Therapeutic Effect of Ciprofloxacin and Compound of Propolis and Ciprofloxacin on men with chronic bacterial prostatitis

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## ABSTRACT

**Background:** Despite the high prevalence and large number of studies on chronic bacterial prostatitis, no effective treatment has been found for this disease.

**Aim:** To compare the therapeutic effect of ciprofloxacin and the combination of propolis and ciprofloxacin on patients with chronic bacterial prostatitis.

**Methods:** This study was performed as a single-blind randomized clinical trial. 190 men with chronic bacterial prostatitis in Qom in 2018-2019 who met the inclusion criteria, formed the statistical population of this study and the samples were selected by census of patients with bacterial prostatitis by the available method. The subjects were randomly assigned to 2 groups receiving ciprofloxacin and a combination of ciprofloxacin and propolis. Blood and urine sampling was performed at the beginning of the study and at the end of the 30-day treatment period. Data analysis was performed using SPSS software version 16 and the significance level was considered to be less than 0.05.

**Results:** The data obtained from WBC and ESR analysis of patients in both groups before and after the study did not show a significant difference. In the study of International Prostatic Symptoms Score, there was no significant difference between the severity of symptoms before treatment in different parameters, but after studying the severity of symptoms and their improvement showed a significant difference. In the first group, 45.7% but in the propolis group, 63.5% improvement was achieved. Based on the pain measurement criteria, the severity of pelvic pain in the two groups before the study was not significantly different, but after the study, the observed difference between the two groups was significant. Based on the results, the rate of pain relief in the first group was 51% and in the second group was 65.8%.

**Conclusion:** Propolis as an anti-inflammatory and immune system booster, antimicrobial, antioxidant, anti-tumor, without any side effects can be used in the treatment of chronic infections and inflammation.

**Keywords:** Ciprofloxacin, Propolis, Chronic bacterial prostatitis.

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## INTRODUCTION

Chronic bacterial prostatitis is one of the most common urological diseases which there is little information about the cause of the disease and its treatment methods. This disease reduces the quality of life of patients by causing pain in the pelvic and genital area. The prevalence of prostatitis in the United States is 10%<sup>1</sup>. It is estimated that half of men suffer from prostatitis symptoms during their lifetime and are treated<sup>2</sup>. Anatomical and neurophysiological obstruction of the urinary tract causes urinary incontinence and prostatitis syndrome, and on the other hand, urinary reflux or possibly the entry of bacteria into the prostate is the most important mechanism of prostatitis<sup>3</sup>. Traditionally, prostatitis has been associated with inflammation of the prostate gland and infection and mood disorders<sup>4</sup>. In a valid classification system, prostatitis can be divided into four categories: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis / chronic pain syndrome, and asymptomatic prostatitis<sup>5</sup>. Culture of patient's urine sample, clinical signs and blood sample are used to diagnose of chronic bacterial prostatitis<sup>6</sup>. Despite its high prevalence and large volume of research, no effective treatment has been introduced for chronic bacterial prostatitis<sup>7</sup>. In general, the recommended

treatment for chronic bacterial prostatitis is antibiotics. Of course, the use of antibiotics is controversial, especially since no bacteria have been isolated from urine samples in patients with bacterial prostatitis<sup>4</sup>.

Because of prostate blood is intact in men with chronic prostatitis, high-pka, lipid-soluble antibiotics should be selected. Antibiotics with these properties are include sulfates, quinolones, macrolides, and tetracyclines<sup>8</sup>. Ciprofloxacin is the most common antibiotic used to treat chronic bacterial prostatitis. Introduce of fluoroquinolone antibiotics, especially ciprofloxacin, made it possible to effectively treat urinary tract infections. Unfortunately, shortly after the introduction of these drugs to treat acute bacterial infections, some bacterial strains involved in urinary tract infections became rapidly resistant to these antibiotics<sup>9</sup>. Nowadays, Escherichia coli resistance to ciprofloxacin is increasing. In studies conducted in different regions of the country, the resistance of Escherichia coli to ciprofloxacin has been reported between 10.2 - 85%<sup>10-12</sup>. In a meta-analysis study to determine the resistance of Escherichia coli to ciprofloxacin by Fasugba et al., It was reported that the resistance of Escherichia coli in nosocomial infections was 0.38 and in community-acquired infections was 0.27. The highest resistance to ciprofloxacin was observed in developing countries. Also, over time and

in more recent studies than in previous studies, more resistance was reported to this antibiotic<sup>13</sup>. Therefore, newer and more harmless substances are needed in the treatment of prostatitis, which have the greatest antibacterial effect and at the same time prevent antibiotic resistance. One of the new issues that needs further research is the use of propolis as a drug supplement.

Propolis is a substance similar to beeswax (*cera alba*) and is produced by bees, whose appearance is very different due to the involvement of many factors. It is usually pasty and varies in color from green, red to dark brown. Propolis has a pleasant odor and adhesive properties due to its strong reaction with skin fats and proteins<sup>14</sup>. The chemical composition of this substance is very complex depending on the plant source and local flora, and more than 300 compounds have been identified in propolis samples. Propolis contains various amounts of aliphatic and aromatic acids, esters, flavonoids, sugars, glycerol, vitamins, minerals and amino acids. Propolis as an antimicrobial, antioxidant, anti-ulcer, anti-tumor, anti-inflammatory, antihypertensive and immune enhancer, and all studies on this substance have not shown any specific side effects. In a study aimed at investigating the effect of propolis on inhibiting the growth of bacteria isolated from the urinary tract in patients with urinary tract infections compared to conventional antibiotics, the results showed that propolis extract was better antibacterial at 50 and 100 mg than common antibiotics<sup>9</sup>. Therefore, according to the above and considering the need to find more effective and less dangerous drugs in the treatment of prostatitis or optimizing the use of doses of available antibiotics and at the same time increase the therapeutic efficiency of these antibiotics and according to little studies on propolis, especially as a complementary drug in the treatment of prostatitis, in the present study, the therapeutic effect of propolis and ciprofloxacin was compared on patients with prostatitis.

## MATERIALS AND METHODS

**Participants:** The present study was a single-blind randomized clinical trial performed using patients with chronic bacterial prostatitis. The samples to participate in this study were selected by easy sampling of men with chronic bacterial prostatitis referred to Kamkar-Arabnia Hospital in Qom in 2018-2019 who met the inclusion criteria and completed the informed consent form. Patients were randomly assigned to 2 groups of parallel treatment and the samples were examined for 30 days. Inclusion criteria were: men with chronic bacterial prostatitis, age between 18 and 60 years<sup>15</sup>, first-time lower urinary tract infection, no chronic disease, don't use alcohol, don't take other antibiotics. Exclusion criteria were: patients with immunodeficiency, diabetics, recent history of urinary tract surgery, having urinary tract stones, anatomical disorders of the urinary tract, patients with severe complications and severe nausea and vomiting due to intolerance of oral drug and allergy to ciprofloxacin and propolis. Finally, according to the study of Yousefi et al<sup>12</sup> and based on the variable of mean urinary frequency, the minimum required sample size in each group was 95.

**Sampling method:** Samples were collected in this study

by simple method. Diagnosis of lower urinary tract infection was confirmed by history, clinical examination (frequent urination and burning) and urine culture (more than  $10^5$  bacteria per ml). The blood and urine sampling process was performed as simple non-probability sampling and continued until the completion of the required minimum sample size in accordance with the objectives of the study. The selected samples were then randomly divided into two groups. The first group, which was considered as the control group, was underwent standard drug treatment with oral ciprofloxacin made by Razak Pharmaceutical Company at a dose of 500 mg and placebo made by Retus Mashhad Company (one dose of ciprofloxacin every 12 hours and one placebo dose) for 30 days<sup>14</sup>. The second group was treated similarly to the first group, oral ciprofloxacin, made by Razak Pharmaceutical Company was used at a dose of 500 mg every 12 hours for 30 days, with the difference that the patients in this group received propolis made by Rotus Mashhad Company at a dose of 500 mg one hour after ciprofloxacin consumption<sup>12</sup>. At the end of the 30-day treatment period, blood and urine samples were taken again from patients who had completed the treatment period.

**Statistical analysis:** In order to analyze the data obtained from the present study, central criteria and dispersion were reported along with tables and graphs in the descriptive statistics section. To compare the number of improved individuals in the two groups, considering that the nominal response variable is two-state, chi-square test or Fisher's exact test was used (if there is a frequency of at least 20% less than 5). McNemar nonparametric test was used to compare each group before and after the intervention due to the nominal response. The data obtained were then analyzed by SPSS-16. The significance level was considered to be less than 0.05.

## RESULTS

In the results of this study, the mean age of patients in the first group (receiving ciprofloxacin) was  $31 \pm 4$  years and the second group (receiving a combination of ciprofloxacin and propolis) was calculated to be  $30 \pm 5$  years, which in this respect, there was no significantly different between the groups ( $P > 0.05$ ). The data obtained from the WBC analysis of patients in both groups before and after the study did not show a significant difference and also the ESR of patients in both groups was similar (Table 1). All patients had negative culture after treatment.

In the study of International Prostatic Symptoms Score (IPSS), there was no significant difference between the severity of symptoms before treatment in different parameters, but after a month of study, the severity of symptoms and their improvement showed a significant difference (Table 2).

Recovery was achieved in both ciprofloxacin and ciprofloxacin with propolis groups. With the difference that in the first group 45.7% but in the propolis receptor group 63.5% improvement was obtained which according to the statistical analysis there was a significant difference in this regard, between the two groups. Based on the 10- Point pain rating scale, the severity of pelvic pain before the study was similar in the two groups, but after the study, the

observed difference was significant between the two groups (Table 3). Based on the results, the rate of pain relief in the first and second groups were 51% and 65.8%, respectively.

Table 1. Comparison of WBC and ESR values before and after the intervention in the studied groups

Sampling time	Measured parameter	Studied group		P- value
		Ciprofloxacin	Ciprofloxacin + Propolis	
Before the intervention	WBC	$7 \times 10^3 \pm 400$	$65 \times 10^3 \pm 600$	>0.05
	ESR	$12 \pm 5$	$10 \pm 7$	>0.05
After the intervention	WBC	$65 \times 10^3 \pm 700$	$7 \times 10^3 \pm 400$	>0.05
	ESR	$8 \pm 9$	$9 \pm 5$	>0.05

Table 2. IPSS symptoms before and after the study in the two groups

Symptoms	Ciprofloxacin		Ciprofloxacin + Propolis		P- value	
	Before	After	Before	After	Before	After
Dysuria	4	3	4	1	>0.05	<0.05
Frequency	5	3	5	1	>0.05	<0.05
Nocturia	3	2	4	1.5	>0.05	<0.05
Narrowing	3	1	3	2	>0.05	<0.05
Straining	4	2	5	1	>0.05	<0.05
Terminal dribbling	4	2	5	3	>0.05	<0.05
	23	13	26	9.5		

Table 3. Improvement of pain in both groups before and after the study

	Ciprofloxacin		Ciprofloxacin + Propolis		P- value	
	Before	After	Before	After	Before	After
Pain scale	6.3	3.2	7.3	2.5	>0.05	<0.05

## DISCUSSION

In this study, the effects of propolis was significant according to several previous studies. In one study, the effect of propolis on bacteria isolated from urinary tract infections was reported in 5 volunteers and after one week of taking propolis capsules, the antibacterial activity of propolis was significant compared to placebo<sup>1</sup>. In another study, ciprofloxacin was not effective in long-term treatments for patients with urinary tract infections and it was suggested that in the study population, treatment of Enterococcus faecalis infections with ampicillin, imipenem and vancomycin antibiotics should be a priority<sup>7</sup>. The results of another study showed that propolis was more effective than honey in fighting bacterial infections. On the other hand, it was reported that Escherichia coli is more resistant than Staphylococcus aureus and higher concentrations of propolis and honey are needed to control it<sup>2</sup>. In a similar study, it was reported that propolis could be used as an adjunct or even the main drug - in situations where antibiotics do not respond - to inhibit bacterial growth<sup>3</sup>. In a study conducted by the author (Dr. Mohammad Heidari) in 2014, significant benefits of honey were reported in the treatment of Fournier gangrene at Shohada Hospital in Khorramabad<sup>16</sup>. Another study by the same author in 2012 reported acute bacterial resistance to ciprofloxacin in Shohada Hospital<sup>17,18</sup>.

In a study by Król et al. propolis has been proposed as a product of bee activity, known for centuries due to its unique biological and medicinal properties. The role of this substance in reducing the amount of free radicals in burn wounds has been proven, and other studies have shown its ability to play roles such as antibacterial, anti-inflammatory and anesthetic properties in complementary medicine<sup>19</sup>. In

a study by Kucharzewski et al<sup>20</sup>, this substance was introduced as an antioxidant with immunomodulatory properties. Other studies have described the effects of propolis on the treatment of burns, venous ulcers, osteoarthritis, and postoperative wound complications. Other articles have reported on the therapeutic effects of propolis on cancer, oral and cardiovascular diseases. Hojjat Alishahi in a descriptive-analytical study in 2015, investigated the frequency of resistant genes to ciprofloxacin (gmrA and gmrB) in Escherichia coli isolates from urinary tract infection in Fars Estahban hospital and the results indicate the presence of resistant gene to fluoroquinolone (gmrB) in the studied Escherichia coli isolates; of 224 isolates, 88 were resistant to ciprofloxacin<sup>4</sup>. Erfanian studied the effects of oral ciprofloxacin and injectable ceftriaxone in a clinical trial in 2007. In this study, 47 female patients with pyelonephritis were randomly selected and treated with one of the injectable ceftriaxone or oral ciprofloxacin regimens. The results of this study showed that the use of oral ciprofloxacin is effective in the treatment of uncomplicated acute pyelonephritis and this drug is equivalent to injectable ceftriaxone, although symptoms of recovery and fever appear later<sup>6</sup>. The results of a study aimed at evaluating the effect of single-dose treatment and seven-day treatment of ciprofloxacin in women with lower urinary tract infections, showed that there is no significant difference between single-dose and seven-day treatment and the effect of ciprofloxacin is the same<sup>8</sup>. As mentioned in this study, the effects of propolis are significant considering the extensive studies that have been done before. While no side effects have been reported for this substance in this study and previous studies, it is recommended that this substance be used to treat chronic infections and inflammation.

## CONCLUSION

Propolis can be effective as an anti-inflammatory and immune system booster, antimicrobial, antioxidant and anti-tumor, although more studies are needed.

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