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Original Article

Transcutaneous electrical nerve stimulation combined with levofloxacin and tamsulosin for patients with chronic prostatitis: clinical efficacy and changes in serum factors

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Abstract: Objective: To analyze the effects of transcutaneous electrical nerve stimulation (TENS) combined with levofloxacin (0.1 g, twice daily) and tamsulosin (0.2 mg, once daily) on clinical efficacy and serum factors in patients with chronic prostatitis (CP). Methods: A retrospective analysis was conducted on 105 patients with CP who received treatment at Hangzhou Lin'an District Hospital of Traditional Chinese Medicine from February 2020 to December 2022. Among them, 47 patients received levofloxacin and tamsulosin were included in a drug group (DG), and 58 patients received additional TENS therapy (frequency: 1/4/1 Hz+80/120/80 Hz; pulse width: 270/230/270 μs+120/80/120 μs; waveform: square and continuous waveforms) were included in a joint group (JG). The changes in the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI), international prostate symptom score (IPSS), and the levels of inflammatory and pain-causing factors were compared between the two groups before and after treatment. The clinical efficacy was compared between the two groups after treatment. Moreover, the incidence of adverse reactions was compared between the two groups. Results: After treatment, the scores of NIH-CPSI and IPSS, and the levels of IL-6, CRP, TNF-α, IL-1β, 5-hydroxytryptamine, substance P, and dynorphin in the JG were obviously lower than those in the DG ($P<0.001$). The clinical response rate in the DG was obviously lower than that in the JG ($P=0.006$, Table 2). There was no difference in total incidence of adverse reactions between the two groups ($P=0.801$). Conclusion: Compared to medication alone (levofloxacin and tamsulosin), the combination of TENS with levofloxacin and tamsulosin can reduce the levels of inflammatory and pain-causing factors in patients, and improve the efficacy. Importantly, it has been observed that this combination therapy does not lead to an increase in adverse reactions and is considered to be safe for patients.

Keywords: Transcutaneous electrical nerve stimulation, levofloxacin, tamsulosin, chronic prostatitis, clinical efficacy

Introduction

Prostatitis is a prevalent urological condition, known for its complex etiology, diverse symptoms, difficult recovery, and high recurrence rates [1]. Furthermore, many individuals with prostatitis experience additional issues concerning their quality of life, as well as physical and mental well-being [2]. Studies [3] have shown that the incidence of chronic prostatitis (CP) in men is 4.5-9%, and the recurrence rate can reach 50% with the increase of age. Approximately half of adult men may experience prostatitis at some stage in their lives. Study has shown that the prevalence of prostatitis ranges between 6.0% and 32.9%, with two onset peaks at the age of 30-40 years and 61-70 years [4].

CP, also known as type III prostatitis in the classification of the National Institutes of Health, is one of the most common and complex urinary system diseases [5]. As the most complex and controversial type of prostatitis, CP accounts for approximately 90-95% of prostatitis cases [6]. Different from bacterial prostatitis, CP, whi-

ch is characterized by pelvic pain, urinary tract abnormalities, sexual dysfunction and a series of psychological symptoms, has not been clearly understood in terms of the exact causes [7]. In recent years, physical therapy has been widely used in andrology, and electrical stimulation therapy has shown good effects in relieving pain and improving quality of life. Compared with drug therapy, electrical stimulation therapy has advantages of simple operation and low incidence of complications [8]. Transcutaneous electrical nerve stimulation (TENS) is a non-invasive therapy that uses low-voltage current to relieve pain [9]. It involves applying low-voltage electric current by placing electrodes on the skin of the area of pain. TENS works by stimulating the nerves responsible for transmitting pain signals, thereby diminishing the perception of pain [10]. TENS can be used to treat chronic pain, acute pain and pain caused by injury or surgery [11]. At present, there is little research on TENS in the treatment of CP, as it was only mentioned in the research of Sikiru et al. [12] in 2008. The therapeutic effect of TENS on patients with CP and its influence on inflammatory factors in serum are still unclear.

This study aimed to analyze the clinical efficacy of TENS combined with levofloxacin and tamsulosin, as well as the serum cytokine changes in patients with CP.

Materials and methods

Inclusion and exclusion criteria

Inclusion criteria: a) patients who met the diagnostic criteria for CP as per the 2014 edition of *Chinese Diagnosis and Treatment of Urological Diseases Guide* [13], namely, patients with a history of symptoms primarily characterized by urinary frequency and urgency, often accompanied by nocturia or urgency urinary incontinence; b) patients with no abnormalities in physical examination of the urinary reproductive system and the nervous system; c) patients who underwent necessary auxiliary examinations such as urinary system color Doppler ultrasound, routine urinalysis, urine flow rate and showed no abnormalities, or patients who underwent selective auxiliary examinations such as urodynamics if they were suggested to have residual urine in the bladder or abnormal urine flow rate by color Doppler ultrasound; d) patients who were treated for the first time and had not received targeted treatment before; e) patients with complete clinical data; f) patients who received corresponding treatment and outcomes evaluation such as serum examination of 5-hydroxytryptamine (5-HT), substance P (SP), and dynorphin (DYN) levels.

Exclusion criteria: a) patients with malignant tumors; b) patients with a history of transurethral surgery or urethral injury; c) patients with skin allergy, nervous system diseases, or serious systemic diseases; d) patients suffering from acute or chronic urethritis, epididymitis, varicocele, perianal and rectal diseases, or sexually transmitted diseases.

Data collection

The clinical information and relevant indicators of patients were recorded and collected using the electronic medical record system at Hangzhou Lin'an District Hospital of Traditional Chinese Medicine. Clinical data included age, course of disease, body mass index (BMI), marital status, smoking history, alcoholism history and previous medical history. The laboratory indexes included interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), 5-HT, SP and DYN. Other data included clinical efficacy after treatment, the National Institutes of Health chronic prostatitis symptom index (NIH-CPSI) [15], international prostate symptom score (IPSS) [16], and adverse reactions during treatment.

Baseline data

A retrospective analysis was conducted on 194 patients with CP who received treatment at Hangzhou Lin'an District Hospital of Traditional Chinese Medicine from February 2020 to December 2022. Out of these patients, 105 individuals who met the inclusion and exclusion criteria were selected as the study subjects. Among them, 47 patients received levofloxacin and tamsulosin were included in a drug group (DG), and 58 patients received additional TENS therapy were included in a joint group (JG). This research was approved by the Medical Ethics Committee of Hangzhou Lin'an District Hospital of Traditional Chinese Medicine (Ethics batch number: 2020 (LL) 21).

Therapeutic schemes

In the DG, patients were treated according to the 2019 edition of *Chinese Guidelines for Diagnosis and Treatment of Urology and Andrology Diseases* [14]. Patients were given 0.1 g of levofloxacin tablets (Shanghai Huanhua Pharmaceutical Co., LTD., SFDA Approval No. H20133179) orally twice a day, and 0.2 mg of tamsulosin hydrochloride sustained-release capsules (Jiangxi Shanxiang Pharmaceutical Co., LTD., SFDA Approval No. H20213991) once a day, for 8 weeks.

On the basis of drug treatment, patients in the JG were additionally treated with TENS using BioStimBle low-frequency neuromuscular therapy instrument. Two electrodes (5 cm×9 cm) were positioned on the patient's skin. Electrode 1 was placed at the junction of tail corresponding to the outer skin of coccyx and the posterior midline. Electrode 2 was situated 2 cm below the navel at the anterior midline of the lower abdomen. The modulation frequency of TENS therapy was set to 1/4/1 Hz+80/120/80 Hz, the pulse width was set to 270/230/270 μs+120/80/120 μs, and the waveform was set as square wave and continuous wave. The current intensity was adjusted based on the patient's muscle tension and their tolerance for slight pain. TENS therapy was performed once every other day, three times a week for the initial four weeks, and twice a week for the remaining four weeks, amounting to a total of 20 times. Each TENS treatment lasted for 30 minutes.

Detection methods

Before and after treatment, 5 mL of fasting venous blood was drawn from the patients in the early morning, and the separated supernatant was labeled and stored for detection. Serum levels of inflammatory factors, including CRP (Batch No.: ml057570), IL-6 (Batch No.: ml058097), IL-1β (Batch No.: ml058059), and TNF-α (Batch No.: ml077385), as well as serum levels of pain-causing substances including 5-HT (Batch No.: ml057425), SP (Batch No.: ml057693), and DYN (Batch No.: ml037935) were detected by enzyme-linked immunosorbent assay. The kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd.

Efficacy evaluation criteria

Markedly effective: After treatment, the clinical symptoms of the patients basically disappeared, and the NIH-CPSI score decreased by 60-90% compared with that before treatment. Effective: After treatment, the clinical symptoms of the patients improved, and the NIH-CPSI score decreased by 30-59% compared with that before treatment. Ineffective: After treatment, the clinical symptoms of the patients did not show significant improvement or even aggravated, and the NIH-CPSI score decreased by less than 30% compared with that before treatment [17].

Outcome measures

Main outcome measures: The changes in NIH-CPSI and IPSS scores before and after treatment were compared between the two groups. The clinical efficacy was compared between the two groups after treatment. Overall response rate = (markedly effective + effective)/ total number of patients ×100%.

Secondary outcome measures: The levels of inflammatory and pain-causing factors were compared between the two groups before and after treatment. The incidence of adverse reactions during the treatment was compared between the two groups.

Statistical methods

The data were processed using SPSS 26.0. Shapiro-Wilk was used to test the normality of the data, and the measurement data conforming to the normal distribution were expressed by mean ± standard deviation (x±sd). Independent sample t-test was used for inter-group comparison, and paired t-test was used for intra-group comparison. χ^2 test was used to compare the counting data. The statistical significance of the results was determined with $P<0.05$.

Results

Comparison of clinical data

After comparing the clinical data, it was observed that there was no statistically significant difference in age, course of disease, BMI, marital status, smoking history, alcoholism history

Table 1. Clinical data

Factors	Drug group (n=47)	Joint group (n=58)	x^2	P
Age			0.167	0.682
≥50 years	27	31		
<50 years	20	27		
Course of disease			0.076	0.782
≥2 years	19	25		
<2 years	28	33		
BMI			0.332	0.564
≥25 kg/m^2	15	22		
<25 kg/m^2	32	37		
Marital status			1.061	0.588
Married	29	30		
Unmarried	10	16		
Divorced	8	12		
Smoking history			1.175	0.278
Yes	43	49		
No	4	9		
Alcoholism history			0.616	0.432
Yes	11	10		
No	36	48		
Previous medical history				
Hypertension	15	17	0.083	0.773
Diabetes	12	10	1.077	0.299

BMI: body mass index.

and previous medical history between the two groups (P>0.05, **Table 1**).

Changes in NIH-CPSI and IPSS scores

There was no difference in the NIH-CPSI and IPSS scores between the two groups before treatment (P>0.05). After treatment, the NIH-CPSI and IPSS scores of the two groups were significantly lower than those before treatment (P<0.01). Further comparison showed that the scores of NIH-CPSI and IPSS in the JG were obviously lower than those in the DG after treatment (P<0.001, **Figure 1**).

Changes in serum inflammatory factors

There was no difference in the levels of IL-6, CRP, TNF-α and IL-1β between the two groups before treatment (P>0.05). After treatment, the levels of IL-6, CRP, TNF-α and IL-1β were significantly lower than those before treatment in both groups (P<0.001). Further comparison showed that the levels of IL-6, CRP, TNF-α and IL-1β in the JG were significantly lower than those in the DG after treatment (P<0.001, **Figure 2**).

Changes in pain-causing factors

There was no difference in the levels of 5-HT, SP and DYN between the two groups before treatment (P>0.05). After treatment, the levels of 5-HT, SP and DYN were significantly lower than those before treatment in both groups (P<0.001). Further comparison showed that the levels of 5-HT, SP and DYN in the JG were obviously lower than those in the DG after treatment (P<0.001, **Figure 3**).

Evaluation of clinical efficacy

The clinical effective rate of the DG was obviously lower than that of the JG (P=0.006, **Table 2**).

Adverse reactions

There was no significant difference in the total incidence of adverse reactions between the two groups (P= 0.801, **Table 3**).

Discussion

CP is a relatively common condition affecting the male urinary system [18]. However, the exact causes and mechanisms of CP are not completely understood in clinical practice. Current studies mainly focus on autoimmune, pathogen infection, urinary dysfunction, psychological factors and neuroendocrine factors [19]. Clinical studies have revealed that patients with CP frequently experience erectile dysfunction, and a significant number of patients also suffer from depression and anxiety. These psychological conditions can greatly impact the quality of life of individuals affected by CP [20].

Drug therapy is currently the first choice for the treatment of CP [21]. Levofloxacin is a fluoroquinolone antibiotic, which is usually used to treat bacterial infections [22]. Levofloxacin has been found to effectively penetrate prostate tissue, so it is a suitable choice for the treatment of bacterial CP and has a significant effect

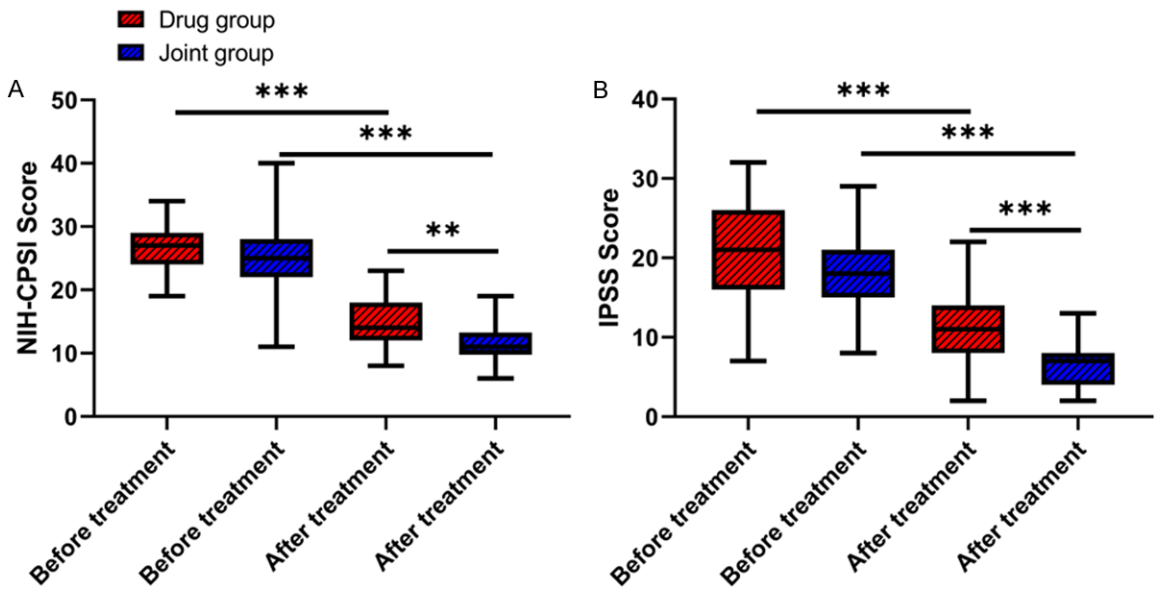

Figure 1. Changes in NIH-CPSI and IPSS scores in patients before and after treatment. A. Changes in NIH-CPSI score before and after treatment. B. Changes in IPSS score before and after treatment. Note: **P<0.01, ***P<0.001; NIH-CPSI: the National Institutes of Health chronic prostatitis symptom index, IPSS: international prostate symptom score.

on gram-negative bacterium [23]. Tamsulosin hydrochloride, an α receptor blocker, is commonly used to alleviate urinary symptoms associated with benign prostatic hyperplasia [24, 25]. Tamsulosin hydrochloride works by relaxing the smooth muscle of the prostate and bladder neck, which can improve urine flow and alleviate discomfort related to CP. Studies [26] have indicated that tamsulosin is beneficial in managing the symptoms of CP. However, it is important to note that tamsulosin hydrochloride in the treatment of CP primarily focuses on symptom relief, rather than curing the disease. TENS, as an alternative therapy of pharmacological treatment for chronic pain, has been applied in the treatment of many diseases, including premature ejaculation, erectile dysfunction and other male diseases [27]. A large number of studies [28, 29] have shown that TENS has a significant analgesic effect and can alleviate diseases by improving inflammatory factors and pain-inducing substances. In this study, we first compared the NIH-CPSI and IPSS scores between the two groups before and after treatment. The results showed that the NIH-CPSI and IPSS scores of patients in the JG were significantly lower than those in the DG after treatment, which indicated that TENS could improve the quality of life, pain and urination symptoms of patients with CP. Studies by Pan et al. [30] and Krakhotkin et al. [31] have demonstrated the effectiveness of different treatment methods in reducing the NIH-CPSI score of patients with CP. Acupuncture combined with extracorporeal shock wave and a multi-mode program guided by UPOINT were both found to be effective in improving symptoms and reducing the NIH-CPSI score. Our research also observed improved NIH-CPSI score in patients. It may be because TENS can stimulate local skin receptors through low-frequency pulse current, inhibit fine fibers, excite coarse fibers, interfere with the afferent pain impulses, relieve pain, and promote the improvement of symptoms, so as to improve the therapeutic effect.

The pathophysiological mechanisms of pain are inflammatory reaction and hyperalgesia [32]. IL-6, CRP, TNF-α and IL-1β are common inflammatory markers in clinic. IL-6 is mainly produced and secreted by macrophages and spinal microglia, and its concentration changes can be indicative of the severity of inflammation [33]. CRP level tends to rise during inflammatory reaction, reflecting the degree of inflammation in the body [34]. TNF-α is mainly produced by neutrophils, macrophages and lymphocytes. It can stimulate dorsal root ganglion neurons, leading to pain-related behavior [35].

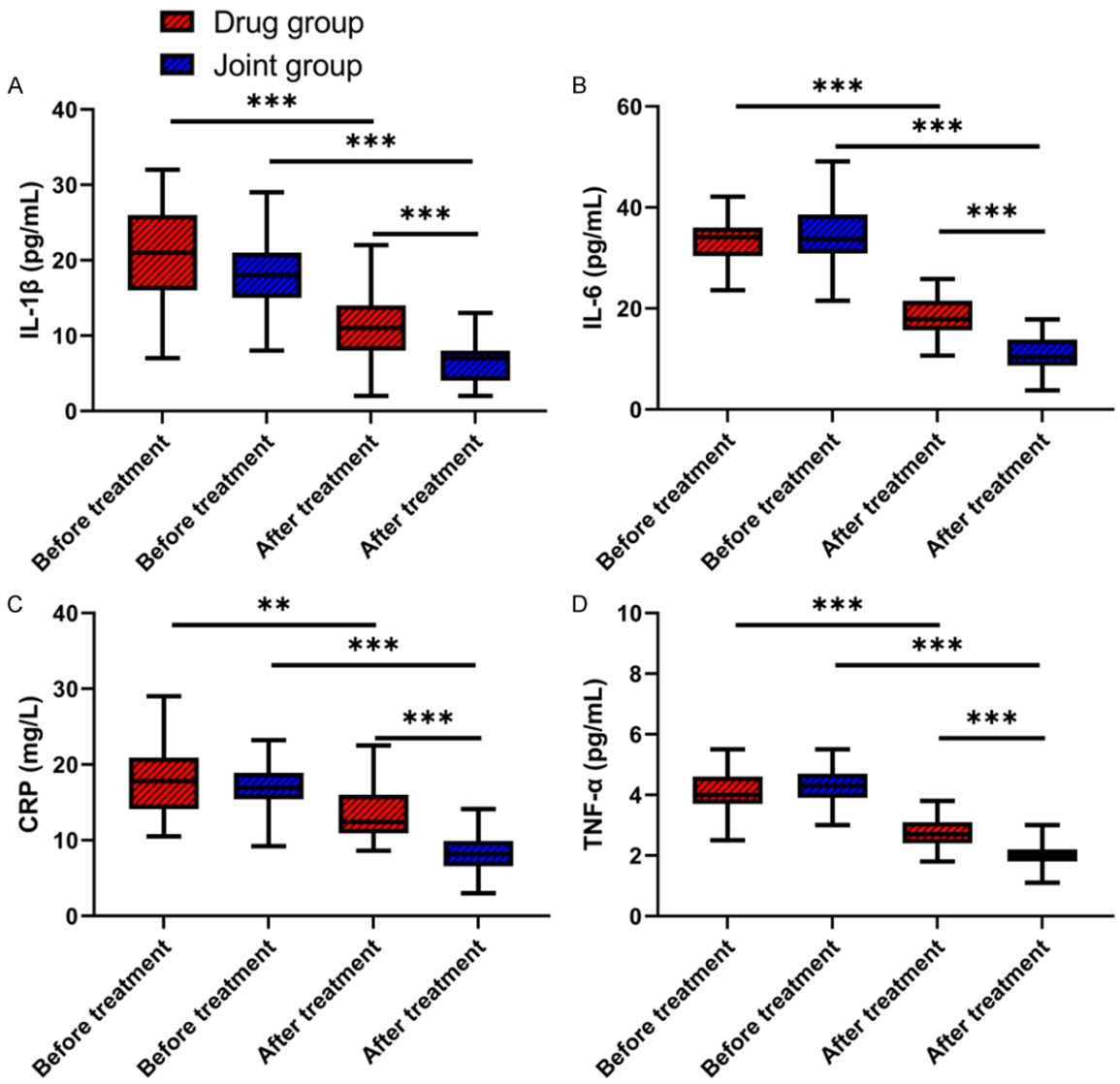

Figure 2. Changes in IL-6, CRP, TNF-α and IL-1β in patients before and after treatment. A. Changes in IL-6 before and after treatment. B. Changes in CRP before and after treatment. C. Changes in TNF-α before and after treatment. D. Changes in IL-1β before and after treatment. Note: **P<0.01, ***P<0.001; IL-6: interleukin-6, CRP: C-reactive protein, TNF-α: tumor necrosis factor-α, IL-1β: interleukin-1β.

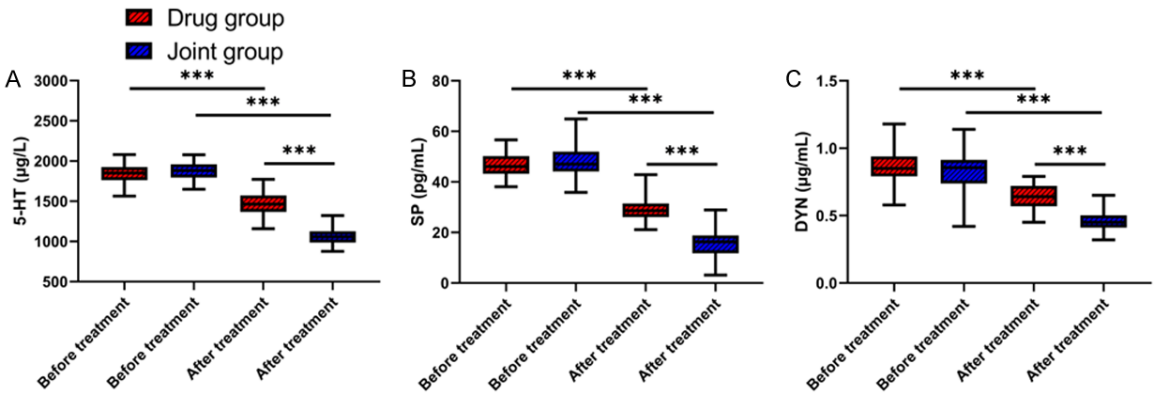

Figure 3. Changes in 5-HT, SP and DYN in patients before and after treatment. A. Changes in 5-HT before and after treatment. B. Changes in SP before and after treatment. C. Changes in DYN before and after treatment. Note: ***P<0.001; 5-HT: 5-hydroxytryptamine, SP: substance P, DYN: dynorphin.

Table 2. Evaluation of clinical efficacy

Groups	Markedly effective	Effective	Ineffective	Overall response rate
Drug group (n=47)	9	27	11	36
Joint group (n=58)	19	32	3	55
X^2		8.120		7.468
P		0.017		0.006

Table 3. Adverse reactions

Groups	Rash	Gastrointestinal discomfort	Palpitation	Dizziness	Elevated transaminase	Total incidence rate
Drug group (n=47)	0	3	3	1	2	9
Joint group (n=58)	2	1	2	3	2	10
X^2	1.652	1.538	0.550	0.656	0.046	0.063
P	0.198	0.215	0.458	0.417	0.829	0.801

IL-1β can indirectly sensitize pain receptors by increasing prostaglandin synthesis and directly act on sensitized receptors to reduce pain regulation, thus inducing pain [36]. In this study, we found that the decreases of IL-6, CRP, TNF-α and Il-1β in patients treated with TENS were more significant than those in the DG. Hyperalgesia and inflammatory reaction are interrelated with the development and progression of pain. Inflammatory markers such as IL-6, CRP, TNF-α and IL-1β can play a role in inducing pain [37]. In addition, the massive secretion of 5-HT, SP and DYN can further promote the release of inflammatory factors, thus aggravating tissue damage [38]. In this study, we found that the decreases of 5-HT, SP and DYN in patients treated with TENS were significant than those in the DG. It may be because TENS can relax blood vessels, improve local blood circulation and balance metabolism, thus promoting the absorption of inflammation. In addition, TENS can activate the coarse fibers in the neuroglia cells of the spinal dorsal horn that can transmit pain and pleasure. This activation leads to the release of inhibitory neurotransmitters and blocks the transmission of pain signals, thus reducing the levels of substances that induce pain. Moreover, the two treatment regimens used in this study did not result in a significant difference in adverse reactions between the two groups, indicating that TENS is generally safe for treating prostatitis.

This study has revealed that TENS combined with levofloxacin and tamsulosin can improve the clinical efficacy in patients with CP and reduce the levels of serum inflammatory and pain-causing factors. However, there are still some limitations in this study. First, as a retrospective study, the sample size was significantly reduced after screening, and whether the results of this single-center study can be generalized needs to be further verified. Second, we did not conduct long-term follow up in the patients. CP is a chronic disease, and whether the two schemes have an impact on the long-term efficacy in patients still needs further experiments to verify. Therefore, we hope to carry out more experiments in the future to improve our research conclusions.

To sum up, TENS combined with drug therapy can reduce the levels of inflammatory and pain-causing factors, and improve the efficacy in patients with CP. Importantly, it has been observed that this combination does not lead to an increase in adverse reactions and is considered to be safe.

Disclosure of conflict of interest

None.

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