

Original Article

Tamsulosin combined with levofloxacin can effectively improve the clinical symptoms and reduce inflammation in CP/CPPS patients

Yizhou Ye, Qian Xu, Mingfa Wan

Department of Urinary Surgery, The First People's Hospital of Tonglu, Hangzhou 311501, Zhejiang Province, China

Received July 7, 2020; Accepted August 26, 2020; Epub January 15, 2021; Published January 30, 2021

Abstract: Background: Both tamsulosin and levofloxacin provide benefits for patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). However, clinical data on the combined treatment using these two drugs are lacking. Objective: This study aimed to explore the effects of tamsulosin hydrochloride combined with levofloxacin on clinical symptoms, inflammation and quality of life of CP/CPPS patients. Methods: Altogether 126 CP/CPPS patients admitted to our hospital from October 2018 to June 2019 were selected as the research objects. Among them, 58 treated with levofloxacin alone were considered as the monotherapy group (MG), and the remaining 68 treated by levofloxacin combined with tamsulosin hydrochloride were seen as the combined group (CG). The clinical efficacy, NIH-CPSI score, International Prostate Symptom Score (IPSS), Self-rating Anxiety Scale (SAS) score, Self-rating Depression Scale (SDS) score and the improvement of inflammation were compared, and the adverse reactions of patients during treatment were recorded. Results: The effective rate of CG was higher than that of MG ($P < 0.05$). After treatment, NIH-CPSI (micturition symptoms, pain and discomfort, quality of life), IPSS, SAS, SDS and other evaluations in the CG were better than those in the MG ($P < 0.05$). The levels of TNF- α , IL-1 β and IL-6 in the CG were dramatically lower than those in the MG ($P < 0.05$). There were no serious adverse reactions between them, and their adverse reactions were similar ($P < 0.05$). Conclusion: Tamsulosin combined with levofloxacin can effectively improve the clinical symptoms, inflammation and negative emotions of CP/CPPS patients without serious adverse reactions.

Keywords: Tamsulosin hydrochloride, levofloxacin, chronic prostatitis, clinical treatment

Introduction

Chronic prostatitis (CP) is a common disease of urinary system, which occurs in young and middle-aged men, and its lifetime prevalence rate is 1.8% to 8.2% [1]. According to the classification of prostatitis by the National Institutes of Health (NIH), it can be divided into four types, among which type III prostatitis, also known as CP/chronic pelvic pain syndrome (CPPS), accounts for 90% of all types [2]. CP/CPPS is defined as pain or discomfort in urology in pelvic area lasting for at least 3 months, or symptoms of urinary system without urinary tract bacterial infection [3]. It is reported that CP/CPPS affects 10%-16% of men in the world [4]. CP/CPPS treatment has always been a difficult challenge. Although there are many therapeutic

methods available, such as α -blockers, antibiotics, anti-inflammatory drugs, antidepressants, physiotherapy and phytotherapy, the effects of these methods are not satisfactory [5, 6]. Therefore, it is still necessary to find a safe and effective therapeutic schedule.

Tamsulosin is a selective α_1 adrenoceptor blocker. Its main mechanism is to selectively block α_1A adrenergic receptor (α_1A AR) in prostate, relax smooth muscle of prostate and smooth muscle of urinary tract, and expands bladder volume, thus treating lower urinary tract symptoms [7]. At present, there are some controversies about the application of antibiotics in CP/CPPS treatment, but those are still the commonly used drugs [8, 9]. Levofloxacin, as a commonly used antibiotic clinically, is one

of quinolones, which has strong broad-spectrum antibacterial effect [10]. A previous animal experiment found that when tamsulosin was combined with levofloxacin, the former could increase the concentration of the latter in the prostate tissue of rats with acute bacterial prostatitis and prolong the action time [11]. Therefore, we suspect that tamsulosin combined with levofloxacin can provide better efficacy for CP/CPPS.

In this study, we mainly analyzed the efficacy and safety of tamsulosin combined with levofloxacin in CP/CPPS treatment. This may help people understand the application value of this combination therapy.

Data and methods

Inclusion and grouping of research objects

Altogether 126 CP/CPPS patients admitted to our hospital from October 2018 to June 2019 were selected as the research objects. Among them, 58 treated with levofloxacin alone were regarded as the monotherapy group (MG), and the remaining 68 treated with levofloxacin combined with tamsulosin hydrochloride were considered as the combined group (CG). Inclusion criteria: patients were in line with NIH diagnostic criteria for CP/CPPS [12]; the course of disease exceeded 3 months; they were 18-65 years old; NIH-CPSI score > 10 points [13]. Exclusion criteria: those received any drug treatment within 4 weeks; those had poor treatment compliance or those were unable to complete various tests in the study; those had incomplete clinical data; those had severe heart, liver and kidney dysfunction; those were allergic to the drugs used; those didn't have mental illness. All subjects signed an informed consent form, and this study was approved by the ethics committee of our hospital.

Treatment

The MG was treated with levofloxacin (Beijing Daiichi-Sankyo Pharmaceutical Co., Ltd., SFDA Approval No. H2000655), 0.1 g/time, twice/day, with warm water. The CG was treated with tamsulosin hydrochloride (Jiangsu Hengrui Pharmaceutical Co., Ltd., SFDA Approval No. H20050392) based on the MG, 0.2 mg/time, once a day. Both groups were treated continu-

ously for two courses of treatment, and two weeks is a continuous treatment.

Outcome measures

Clinical efficacy evaluation: cure: the number of white blood cells detected by prostatic fluid was less than 10 cells/HP, and NIH-CPSI score reduced by $\geq 90\%$ compared with that before treatment; markedly effective: the results of prostatic fluid examination were obviously improved, and NIH-CPSI score decreased by 60%-89%; effective: the results of prostatic fluid examination improved and NIH-CPSI score decreased by 30%-59%; ineffective: the results of prostatic fluid examination did not improve remarkably or even worsened, and NIH-CPSI score decreased by $\leq 30\%$. Total effective rate = (cured number + markedly effective number + effective number)/total number $\times 100\%$.

Urodynamic examination: the urodynamic indexes of patients before and after treatment were recorded, mainly including the changes of maximum urinary flow rate (MFR) and residual urine volume (RVU) of bladder.

Pain and discomfort, urination symptoms and quality of life of patients before and after treatment were evaluated by NIH-CPSI scale [13]. The lower the score was, the better the efficacy was. The prostate symptoms before and after treatment were evaluated by the International Prostate Symptom Score [14] (IPSS), 35 scores in total. The lower the score was, the lighter the clinical symptoms were. Before and after treatment, their anxiety and depression were evaluated by Self-rating Anxiety Scale (SAS) [15] and Self-rating Depression Scale (SDS) [16]. The total scores of both were 100 points, and the higher the score was, the more serious the anxiety was.

Adverse reactions during treatment were recorded, including dizziness, gastrointestinal reaction and tinnitus.

Serum of patients before and after treatment was collected, and the changes of inflammatory factors in serum were detected by double antibody sandwich ELISA. The main inflammatory factors included TNF- α , IL-1 β and IL-6. The kit originated from American Abcam, and the operation process was strictly carried out in view of the instructions.

Table 1. Comparison of general data of patients between both groups

| Group | Monotherapy group (n=58) | Combined group (n=68) | χ^2/t | P |
|------------------------------------|--------------------------|-----------------------|------------|-------|
| Average age (years) | 34.85±5.98 | 35.59±7.11 | 0.533 | 0.626 |
| BMI (kg/m ²) | 23.15±1.33 | 23.36±1.48 | 0.832 | 0.407 |
| Average course of disease (months) | 9.21±5.15 | 10.05±4.68 | 0.659 | 0.511 |
| Smoking history | | | 1.933 | 0.165 |
| Yes | 23 (39.66) | 19 (27.94) | | |
| No | 35 (60.34) | 49 (72.06) | | |
| Alcoholism | | | 0.320 | 0.572 |
| Yes | 18 (31.03) | 18 (26.47) | | |
| No | 40 (68.97) | 50 (73.53) | | |
| Educational level | | | 0.190 | 0.663 |
| < high school | 20 (34.48) | 26 (38.24) | | |
| ≥ high school | 38 (65.52) | 42 (61.76) | | |
| Working | | | 0.325 | 0.569 |
| Yes | 21 (36.21) | 28 (41.18) | | |
| No | 37 (63.79) | 40 (58.82) | | |
| Marital status | | | 0.568 | 0.451 |
| Yes | 40 (68.97) | 51 (75.00) | | |
| No | 18 (31.03) | 17 (25.00) | | |

Table 2. Comparison of clinical efficacy

| Group | Cure | Markedly effective | Effective | Ineffective | Total effective rate |
|--------------------------|------------|--------------------|-----------|-------------|----------------------|
| Monotherapy group (n=58) | 19 (32.76) | 25 (43.10) | 9 (15.52) | 5 (8.62) | 44 (75.86) |
| Combined group (n=68) | 29 (42.65) | 32 (47.06) | 5 (7.35) | 2 (2.94) | 61 (89.71) |
| χ^2 | - | - | - | - | 4.319 |
| P | - | - | - | - | 0.038 |

Statistical analysis

Statistical analysis adopted SPSS 19.0, and data pictures were drawn via GraphPad Prism 7. The counting data were compared by Chi-square test. The measurement data between both groups were compared by independent-samples T test, and the comparison before and after treatment in the same group was compared by paired t-test. Those measurement data between multiple groups were compared by one-way ANOVA, and the accuracy of statistical values was verified by back testing (tukey hsd method). $P < 0.05$ was statistically remarkable.

Results

Comparison of general data

There was no obvious difference between the two groups in age, BMI, smoking history, alco-

holism, educational level, working status and marital status ($P < 0.05$) (**Table 1**).

Comparison of clinical efficacy

After evaluating the efficacy of CP/CPPS patients in both groups, we found that in the MG, 19 cases were cured (32.76), 25 were markedly effective (43.10), 9 were effective (15.52), 5 were ineffective (8.62), and the total effective rate was 75.86%. In the CG, 29 (42.65) cases were cured, 32 (47.06) were markedly effective, 5 (7.35) were effective, 2 (2.94) were ineffective, and the total effective rate was 89.71%. The total effective rate of CG was higher than that of MG ($P < 0.05$) (**Table 2**).

Comparison of urodynamic indexes

The urodynamic indexes of patients before and after treatment showed that the MRF and RVU evaluation results of both groups were similar

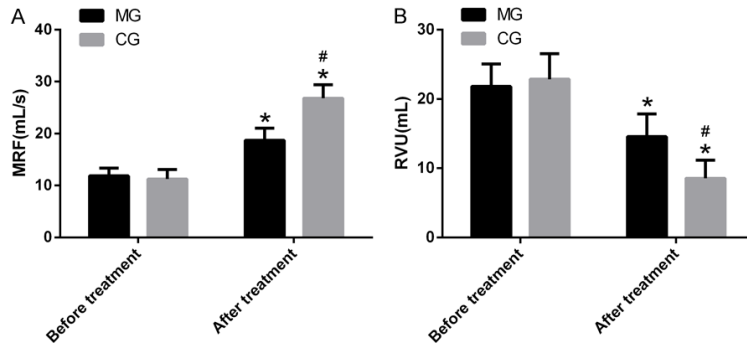


Figure 1. Comparison of urodynamic indexes. A. Changes of MRF levels in both groups before and after treatment; B. Changes of RVU levels in both groups before and after treatment; Note: compared with before treatment, * means $P < 0.05$; compared with MG, # means $P < 0.05$.

before treatment ($P > 0.05$). While after treatment, the MRF and RVU indexes improved to some extent, and these two indexes in the CG were better than those in the MG ($P < 0.05$) (Figure 1).

Comparison of NIH-CPSI scores

Evaluation of NIH-CPSI scores of patients before and after treatment showed that the scores of urination symptoms, pain and quality of life before treatment were similar between both groups ($P > 0.05$). But after treatment, these three scores in the CG were obviously lower than those in the MG ($P < 0.05$) (Figure 2).

Comparison of IPSS, SAS and SDS scores

IPSS, SAS and SDS of patients were evaluated before and after treatment, and the results were similar before treatment ($P > 0.05$). But after treatment, the average IPSS, SAS and SDS in the CG decreased dramatically, and the evaluation results of the CG were better than those in the MG ($P < 0.05$) (Figure 3).

Comparison of adverse reactions

There were no serious complications in the two groups, which could be cured by symptomatic treatment. The total adverse reaction rates of MG and CG were 12.07% and 23.53%, respectively, with no statistical difference ($P > 0.05$) (Table 3).

Comparison of inflammatory factors

After detecting the levels of pro-inflammatory factors in serum of patients before and after

treatment, we found that the levels of $\text{TNF-}\alpha$, $\text{IL-1}\beta$ and IL-6 in both groups were similar before treatment ($P > 0.05$). But after treatment, the three levels of these three decreased dramatically, and the levels in the CG were lower than those in the MG ($P < 0.05$) (Figure 4).

Discussion

This study mainly explored the efficacy and safety of tamsulosin combined with levofloxacin in CP/CPPS treatment. The results showed that this combination therapy was better than levofloxacin alone, because the total effective rate of combined application was higher, and NIH-CPSI (urination symptoms, pain and discomfort, quality of life), IPSS, SAS and SDS scores were also significantly improved.

CP/CPPS is the most common urological disease in men under 50 years old, which is characterized by various pain and inflammation symptoms in pelvic region and seriously affects the quality of life of patients [17]. However, the etiology and pathogenesis of CP/CPPS are still unclear, and doctors often use empirical drugs to control patients' symptoms, among which antibacterial drugs and α -adrenergic receptor antagonists are the two most frequently used drugs [18]. Tamsulosin is one of the drugs commonly used by CP/CPPS patients, which can relieve smooth muscle spasm, reduce urethral pressure, prevent urine from flowing back into prostate and improve urination function [19]. Levofloxacin is a commonly used antibiotic clinically, which can inhibit the activity of bacterial DNA helicase, prevent the synthesis and replication of bacterial DNA and lead to bacterial death [20]. Although both tamsulosin and levofloxacin have been proved to be beneficial to CP/CPPS patients, as far as we know, there is no clinical study on the combination of the two in CP/CPPS treatment. Our results showed that compared with the MG, the CG had higher total effective rate, superior improvement of urodynamic indexes, and better urination symptoms, pain and discomfort scores and IPSS scores in NIH-CPSI scale. Compared with levofloxacin alone, tamsulosin combined with levofloxacin could effectively improve the clinical

Clinical analysis of tamsulosin combined with levofloxacin on CP/CPPS

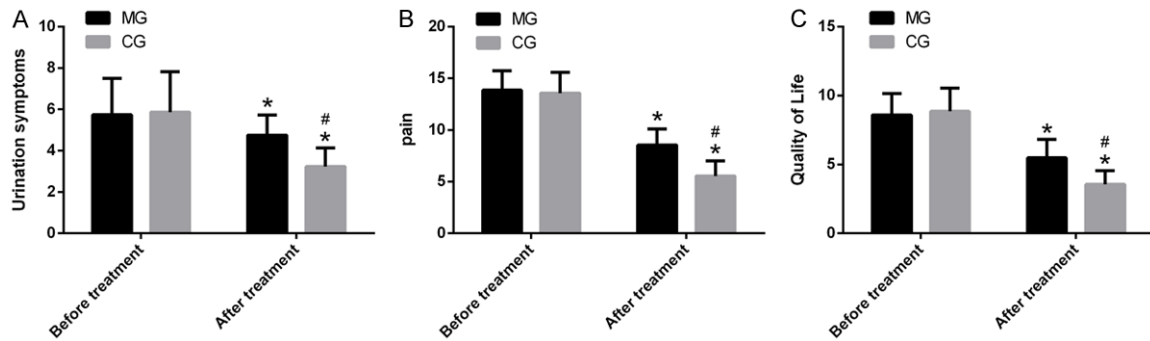


Figure 2. Comparison of NIH-CPSI scores. A. Comparison of micturition symptom scores between both groups before and after treatment; B. Comparison of pain scores between both groups before and after treatment; C. Comparison of quality of life scores between both groups before and after treatment; Note: compared with before treatment, * means $P < 0.05$; compared with MG, # means $P < 0.05$.

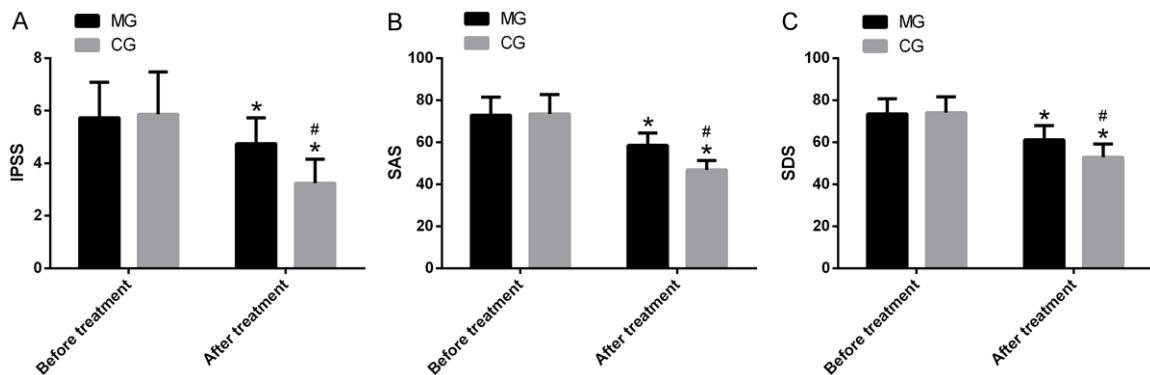


Figure 3. Comparison of IPSS, SAS and SDS scores. A. Comparison of IPSS scores between both groups before and after treatment; B. Comparison of SAS scores between both groups before and after treatment; C. Comparison of SDS scores between both groups before and after treatment; Note: compared with before treatment, * means $P < 0.05$; compared with MG, # means $P < 0.05$.

Table 3. Incidence of adverse reactions

| Group | Monotherapy group (n=58) | Combined group (n=68) | χ^2 | P |
|---------------------------------|--------------------------|-----------------------|----------|-------|
| Dizziness and headache | 3 (5.17) | 5 (7.35) | 0.250 | 0.617 |
| Tinnitus | 1 (1.72) | 3 (4.41) | 0.736 | 0.391 |
| Nausea and vomiting | 2 (3.45) | 8 (11.76) | 2.963 | 0.085 |
| Rash | 1 (1.72) | 2 (2.94) | 0.199 | 0.655 |
| Total number of people affected | 7 (12.07) | 16 (23.53) | 2.755 | 0.097 |

symptoms of patients. The reason may be that tamsulosin and levofloxacin do not interfere with each other and can play their own roles at the same time; in addition, tamsulosin may increase the concentration of levofloxacin in prostate and prolong the duration of its antibacterial activity, thus improving the effect of levofloxacin on pathogenic microorganisms [11], so as to achieve better efficacy. Because CP/CPPS patients are affected by diseases for

a long time, more than 80% patients have psychological problems [21]. Studies have shown that anxiety and depression are more common in CP/CPPS patients, which has a negative impact on their quality of life, rehabilitation and work efficiency [22]. We evaluated the negative emotions of patients in the two groups and found that the scores of SAS and SDS in the CG were lower than those in the MG. This also reflects that the efficacy of tamsulosin com-

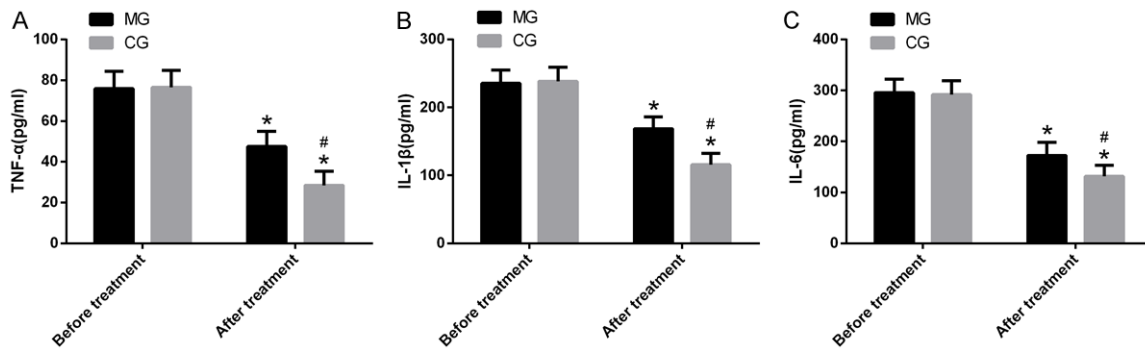


Figure 4. Comparison of inflammatory factors. A. Comparison of TNF- α levels between both groups before and after treatment; B. Comparison of IL-1 β levels between both groups before and after treatment; C. Comparison of IL-6 levels between both groups before and after treatment; Note: compared with before treatment, * means $P < 0.05$; compared with MG, # means $P < 0.05$.

combined with levofloxacin on CP/CPPS is better than that of levofloxacin alone. The adverse reactions of both groups were recorded during treatment. It was found that their adverse reactions were similar, and no serious adverse reactions occurred, which could be cured by symptomatic treatment. This shows that the combination of the two in CP/CPPS treatment will not increase too many adverse reactions.

Chronic inflammation is considered as a vital factor leading to CP/CPPS development, and it is related to chronic pain of patients [23]. Thus, reducing inflammation in patients is considered as one of the directions of CP/CPPS treatment. It was found that CP/CPPS patients showed higher levels of proinflammatory cytokines, such as TNF- α , IL-1 β and IL-6 [24, 25]. After treatment, we detected the levels of proinflammatory factors in both groups, and found that the levels of TNF- α , IL-1 β and IL-6 decreased to a great extent, and the levels of the three in the CG were lower than those in the MG. Tamsulosin may increase the concentration of levofloxacin in patients, thus enhancing the anti-inflammatory effect of levofloxacin.

Nevertheless, there are some shortcomings in this study. Firstly, the best dose of tamsulosin combined with levofloxacin in CP/CPPS treatment has not been explored. Secondly, the long-term clinical results of the two groups were not followed up. What's more, this study did not explore the difference between tamsulosin combined with levofloxacin and tamsulosin alone in CP/CPPS treatment. These shortcomings are expected to be supplemented in future research.

To sum up, tamsulosin combined with levofloxacin can improve the clinical symptoms, inflammation and quality of life of CP/CPPS patients.

Disclosure of conflict of interest

None.

Address correspondence to: Qian Xu, Department of Urinary Surgery, The First People's Hospital of Tonglu, No. 338 Xuesheng Road, Tonglu County, Hangzhou 311501, Zhejiang Province, China. Tel: +86-0571-64399795; E-mail: qianxu263@outlook.com

References

- [1] Holt JD, Garrett WA, McCurry TK and Teichman JM. Common questions about chronic prostatitis. *Am Fam Physician* 2016; 93: 290-296.
- [2] Peng T, Cheng Y, Jin Y, Xu N and Guo T. Acupuncture for chronic prostatitis: a systematic review and meta-analysis protocol. *Medicine (Baltimore)* 2018; 97: e0615.
- [3] Engeler DS, Baranowski AP, Dinis-Oliveira P, Elnail S, Hughes J, Messelink EJ, van Ophoven A and Williams AC; European Association of Urology. The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur Urol* 2013; 64: 431-439.
- [4] Qin Z, Liu Y, Zhou K, Wu J, Pang R, Li N, Xu C, Kwong JSW and Liu Z. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: study protocol for a randomized controlled trial. *Trials* 2017; 18: 616.
- [5] Zhang J, Liang C, Shang X and Li H. Chronic prostatitis/chronic pelvic pain syndrome: a disease or symptom? Current perspectives on diagnosis, treatment, and prognosis. *Am J Mens Health* 2020; 14: 1557988320903200.

- [6] Zhang K, Zeng X, Chen Y, Zhao R, Wang H and Wu J. Therapeutic effects of Qian-Yu decoction and its three extracts on carrageenan-induced chronic prostatitis/chronic pelvic pain syndrome in rats. *BMC Complement Altern Med* 2017; 17: 75.
- [7] Dunn CJ, Matheson A and Faulds DM. Tamsulosin: a review of its pharmacology and therapeutic efficacy in the management of lower urinary tract symptoms. *Drugs Aging* 2002; 19: 135-161.
- [8] Nickel JC, Shoskes DA and Wagenlehner FM. Management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS): the studies, the evidence, and the impact. *World J Urol* 2013; 31: 747-753.
- [9] Nickel JC, Downey J, Johnston B and Clark J; Canadian Prostatitis Research Group. Predictors of patient response to antibiotic therapy for the chronic prostatitis/chronic pelvic pain syndrome: a prospective multicenter clinical trial. *J Urol* 2001; 165: 1539-1544.
- [10] Bano R and Arsalan A. In vitro antibacterial susceptibility of different brands of oral levofloxacin 250 mg tablet against *Staphylococcus aureus* and *Escherichia coli*. *Pak J Pharm Sci* 2018; 31: 2529-2535.
- [11] Qin GD, Xiao MZ, Zhou YD, Yang J, He HX, He Y and Zeng Y. Tamsulosin alters levofloxacin pharmacokinetics in prostates derived from rats with acute bacterial prostatitis. *Asian J Androl* 2013; 15: 254-260.
- [12] Zhao Z, Xuan X, Zhang J, He J and Zeng G. A prospective study on association of prostatic calcifications with sexual dysfunction in men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). *J Sex Med* 2014; 11: 2528-2536.
- [13] Wagenlehner FM, van Till JW, Magri V, Perletti G, Houbiers JG, Weidner W and Nickel JC. National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) symptom evaluation in multinational cohorts of patients with chronic prostatitis/chronic pelvic pain syndrome. *Eur Urol* 2013; 63: 953-959.
- [14] Gregoire JP, Moisan J, Labrecque M, Cusan L and Diamond P. Validation of a French adaptation of the international prostatic symptom score. *Prog Urol* 1996; 6: 240-249.
- [15] Dunstan DA, Scott N and Todd AK. Screening for anxiety and depression: reassessing the utility of the Zung scales. *BMC Psychiatry* 2017; 17: 329.
- [16] Liu N, Liu S, Yu N, Peng Y, Wen Y, Tang J and Kong L. Correlations among psychological resilience, self-efficacy, and negative emotion in acute myocardial infarction patients after percutaneous coronary intervention. *Front Psychiatry* 2018; 9: 1.
- [17] Breser ML, Salazar FC, Rivero VE and Motrich RD. Immunological mechanisms underlying chronic pelvic pain and prostate inflammation in chronic pelvic pain syndrome. *Front Immunol* 2017; 8: 898.
- [18] Qin Z, Wu J, Tian J, Zhou J, Liu Y and Liu Z. Network meta-analysis of the efficacy of acupuncture, alpha-blockers and antibiotics on chronic prostatitis/chronic pelvic pain syndrome. *Sci Rep* 2016; 6: 35737.
- [19] Fawzi A, Kamel M, Salem E, Desoky E, Omran M, Elgalaly H, Sakr A, Maarouf A and Khalil S. Sildenafil citrate in combination with tamsulosin versus tamsulosin monotherapy for management of male lower urinary tract symptoms due to benign prostatic hyperplasia: a randomised, double-blind, placebo-controlled trial. *Arab J Urol* 2017; 15: 53-59.
- [20] Bush LM, Chaparro-Rojas F, Okeh V and Etienne J. Cumulative clinical experience from over a decade of use of levofloxacin in urinary tract infections: critical appraisal and role in therapy. *Infect Drug Resist* 2011; 4: 177-189.
- [21] Mo MQ, Long LL, Xie WL, Chen S, Zhang WH, Luo CQ and Deng LW. Sexual dysfunctions and psychological disorders associated with type IIIa chronic prostatitis: a clinical survey in China. *Int Urol Nephrol* 2014; 46: 2255-2261.
- [22] Wang J, Liang K, Sun H, Li L, Wang H and Cao J. Psychotherapy combined with drug therapy in patients with category III chronic prostatitis/chronic pelvic pain syndrome: a randomized controlled trial. *Int J Urol* 2018; 25: 710-715.
- [23] Lin Y, Bai Y, Liu P, Yang X, Qin W, Gu J, Ding D, Tian J and Wang M. Alterations in regional homogeneity of resting-state cerebral activity in patients with chronic prostatitis/chronic pelvic pain syndrome. *PLoS One* 2017; 12: e0184896.
- [24] Hu C, Yang H, Zhao Y, Chen X, Dong Y, Li L, Dong Y, Cui J, Zhu T, Zheng P, Lin CS and Dai J. The role of inflammatory cytokines and ERK1/2 signaling in chronic prostatitis/chronic pelvic pain syndrome with related mental health disorders. *Sci Rep* 2016; 6: 28608.
- [25] Huang TR, Li W and Peng B. Correlation of inflammatory mediators in prostatic secretion with chronic prostatitis and chronic pelvic pain syndrome. *Andrologia* 2018; 50.