Chin J Integr Med 2021 Mar;27(3):170-176

Chinese Journal of Integrative Medicine

Available online at link.springer.com/journal/11655
Journal homepage: www.cjim.cn/zxyjhen/zxyjhen/ch/index.aspx
E-mail: cjim_en@cjim.cn

Original Article

Effectiveness and Safety of Umbilicus Treatment with Modified Dinggui Powder (加味丁桂散) in Patients with Chronic Nonbacterial Prostatitis: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial*

HUANG Hai[1], ZHOU Min-jie[2], WANG Ke-xie[2], YU Chao[3], WANG Yu-hang[4], JI Jun[4], PAN Wen[5], YING Jian[3,4], and ZHAO Ling[5]

ABSTRACT **Objective:** To evaluate the effectiveness and safety of Chinese herbal external umbilicus treatment with Modified Dinggui Powder (加味丁桂散, MDGP) in patients with chronic nonbacterial prostatitis (CNP). **Methods:** A randomized, double-blind, placebo-controlled clinical trial was conducted among 72 patients with CNP. Participants were randomly allocated to a treatment group and a placebo group using computer software in a 1:1 ratio, and received either MDGP external umbilicus treatment (MDGP group, 36 cases) or placebo (control group, 36 cases) at acupoints Shenque (CV 8), twice a week for 4 weeks. In addtion, patients all received herbal medicine treatment twice a day for 4 weeks. The primary outcome was the US National Institutes of Health Chronic Prostatitis Symptom Scores Index (NIH-CPSI) with a questionnaire at weeks 2 and 4. The secondary outcomes including prostatic fluid examination (white blood cells and lecithin bodies), the clinical efficacy evaluation, and the adverse events were also assessed during the entire trial. **Results:** The NIH-CPSI scores regarding pain or discomfort scores showed greater improvement in the MDGP group than placebo control group at weeks 2 (P=0.001) and week 4 (P=0.004), respectively. NIH-CPSI scores of symptom severity, total scores and leukocytes number in the prostatic fluid in the MDGP group were significantly improved (P<0.05). There was no statistical difference in the urinary symptoms, quality of life, lecithin and other scores between two groups (P>0.05). The clinical effective rate was 73.53% (25/34) in the MDGP group, which was significally higher than the placebo control group with 48.39% (25/31, P<0.05). Patients were blinded successfully, and no serious adverse effects were found during the trial. **Conclusion:** A 4-week course of umbilicus treatment with modified Dinggui Powder seems to relieve pain and symptom severity effectively and increase the amount of leukocytes number in patients with CNP (Trial registration No. ChiCTR1800014687).

KEYWORDS Modified Dinggui Powder, umbilicus treatment, chronic nonbacterial prostatitis, randomized, placebo-controlled trial

Chronic prostatitis is the most common disease in urological clinics. About half of male develop prostatitis symptoms at some stage of their lives, which seriously affects their quality of life and mental health. Prostatitis-like symptoms, especially pelvic pain, occur with a prevalence of about 8%.[1] Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is characterized by perineal, lower abdominal, penile and ejaculatory pains, frequently accompanied by urinary symptoms and/or voiding dysfunction.[2] The pathogenesis of this disease has not yet been clearly stated. Clinically, the abuse of antibiotics is very serious and the therapeutic effect cannot be satisfied with patients and doctors.

The treatment of CP/CPPS mainly aimed at

*Supported by the Shanghai Three-Year Development Plan Project for Traditional Chinese Medicine [No. ZY (2018–2020)-CCCX-2001-05]

1. Department of Joint Surgery, Guanghua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai (200052), China; 2. Department of Vascular Surgery, Shanghai Traditional Chinese Medicine Integrated Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai (200082), China; 3. Department of Urology and Andrology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai (200032), China; 4. Shanghai Qigong Research Institute, Shanghai University of Traditional Chinese Medicine, Shanghai (200030), China; 5. School of Acupuncture-Moxbustion and Tuina, Shanghai University of Traditional Chinese Medicine, Shanghai (201203), China
Correspondence to: Prof. YING Jian, E-mail: yingjian03@sina.com

DOI: https://doi.org/10.1007/s11655-020-3258-5

alleviation and control of clinic symptom. Over the years, studies showed that Chinese medicine (CM) treatment can be used to alleviate some chronic nonbacterial prostatitis (CNP) symptoms. Increasing evidence suggests that acupuncture could improve symptoms and benefit men who suffered from CP/CPPS.[3-8]

Chinese herbal external umbilicus therapy has been widely used in various clinical fields recently.[9] Umbilicus is one of the most important signs of the body.[10] According to CM theory, the umbilicus is called CV 8 (Shenque) point. Shen refers to the soul, and que refers to the palace gate. Umbilicus area has the highest body surface temperature.[11] The relationship between the umbilicus and circulatory system is inherently formed.[12] Modern studies have found that the structure of umbilicus would be beneficial to the absorption of external medicine.[13] Research showed that bioavailability through the forearm administration is only 1/6 of that administered via the umbilicus.[14] The purpose of this placebo controlled, clinical trial was to confirm whether a 4-week modified Dinggui Powder (加味丁桂散, MDGP) umbilicus treatment is effecttive and safe in patients with CNP.

METHODS

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: (1) male patients, aged 20–50 years old who met the diagnostic criteria according to *Urology* edited by Dr. WU Jie-ping.[15] (2) CNP duration lasted more than 3 months; (3) willing to sign informed consent. Patients were excluded if (1) with acute prostatitis or urinary tract infection, urethritis patients; (2) with benign prostatic hyperplasia and prostate cancer; (3) with local pain due to urinary calculi, varicocele, colorectal disease, epididymitis, groin, lumbar disease, etc; and (4) patients who suffered from severe heart, liver, kidney and hematopoietic system diseases or mental disorder.

Sample Size Estimate

The primary endpoint was the decrease of National Institutes of Health Chronic prostatitis Symptom Scores Index (NIH-CPSI) at week 4. Given the lack of research in this field, it was difficult to estimate the effect of real umbilicus treatment compared to control. Our trial was designed based on previously reported randomized, placebo-controlled trials (RCTs) of acupuncture *versus* sham control for CP.[16,17] However, it is recommended that a minimum of 30 participants should be required to achieve sufficient precision to enable sample size calculation for subsequent study.[18] Therefore, we planned to recruit 60 participants, which allow the completion of data collection from 30 subjects, with 75% participant retention rate, we enrolled 36 each group to allow for a possible 20% dropout.

Participants

Recruitment of patients started in February 2018 and the last patient was screened and enrolled in July 2018. The trial concluded in August 2018. The study was carried out at outpatient clinics in Shanghai Longhua Hospital and Qigong Institute Medical Clinic. Participants were recruited by advertisements in local communities. The study protocol was approved by the Medical Ethics Committee of Longhua Hospital (No. 2014LCSY30), and registered in the China Clinical Trials Registration Center (Trial registration number: ChiCTR1800014687).

Randomization and Blinding

After a brief telephone screening, patients were scheduled to an initial visit in which they read, understood, and signed an informed consent and underwent a brief examination by a physician. Eligible patients were randomly assigned to receive either umbilicus treatment with MDGP or placebo control and scheduled for baseline assessment and treatment. We had all necessary consent from any patients involved in the trial, including consent to participate in the trial. Randomization was generated using computer software. Allocation concealment was ensured with letter codes that disguised patient names and groups. The practitioners, acupuncturists with at least 5 years of training in acupuncture and moxibustion, performed the treatment. Because MDGP and placebo powders appeared to be identical, practitioners and patients were blinded to treatment assignment. The assessors were responsible for the outcome assessment and unknowing of the participants' group. Blinding success was validated at the end of the study.

Herbs Preparation

MDGP was applied in participants of treatment group. *Flos Caryophylli* (No.180602), *Cortex Cinnamomi* (No.180501) and *Cortex Phellodendri* (No.180801) were purchased from Shanghai Longhua Hospital Pharmacy, and made to fine with high-speed

Chin J Integr Med 2021 Mar;27(3):170-176

crusher. With 15 g of each herb, *Flos Caryophylli*, *Cortex Cinnamomi* and *Cortex Phellodendri* were fully mixed with 10 mL peppermint oil, and the mixed herbs was bottled and sealed tightly. Then it was put into the cool dry place away from light to avoid evaporation. The placebo power consisted of starch (30 g, Hebei Jinshahe Flour Industry Group Co., Ltd) and coffee grounds (15 g, Starbucks) were mixed with 10 mL of peppercmint oil, and the mixture was bottled and sealed tightly. Afterwards, it was put in the cool dry place away from light to avoid evaporation. It is uniformly powdered by professionals who have the qualification of practicing Chinese pharmacist. The active and placebo powder were similar in appearance and aroma thus made it possible for blinding. The placebo powder was brownish and accompanied by a mint flavor consisted of starch and coffee grounds, resembles the active MDGP in appearance. Both groups were mixed with peppermint oil and had a unique similar mint aroma. Patients and practitioners were all blinded.

Interventions

The acupoint CV 8 is located in the umbilicus fossa.[19] Patients were supine during treatment. Patients in both groups were treated as following: First, practitioners gently cleaned the umbilical fossa using warm water, and then dried it with a dry cotton ball. The flavored of 2 g MDPG or placebo powder was taken and placed on the umbilicus. The outer cover was covered with benzalkonium chloride. In each treatment, the powder was kept on the umbilicus for 24 h, twice a week and totally 8 treatments for 4 weeks. All the patients received herbal medicine twice a day for 4 weeks, the same CM physician slightly adjusted the formula of Modified Sanren Decoction (加味三仁汤) weekly based on the patients' syndrome, tongue coating, and pulse.

Outcome Measures

Primary Outcome

NIH-CPSI is a questionnaire commonly used for evaluating prostatitis-like symptoms.[20-22] Assessment of NIH-CPSI is a reliable, convenient, self-administered index, including pain symptoms, urinary symptoms, and quality of life (QoL). The Chinese version of NIH-CPSI was widely used in the previous studies in China[23-25] and be used as the primary outcome and measured at weeks 2 and 4. Two physicians blinded to treatment allocation performed the assessments.

Secondary Outcomes

The secondary outcome was prostate gland fluid examination at baseline and week 4 from first half of the participants (32 cases, 17 from MDGP group and 15 from placebo control group). WBCs in the prostate gland fluid were counted by the slide method and divided into different groups at high magnification (HP): <+, 10/HP; +, 10–20/HP; + +, 21–30/HP; +++, 31–40/HP; >+ + +, 40/HP. The effect on WBCs in prostate gland fluid was defined as follows[26–28]: improved, a decrease of "+"; stable, no change of WBCs; and deteriorated, an increase of "+". Lecithin body in normal range is ⩾75% of normal amount while abnormal range is <75% of normal amount. Lecithin in prostate gland fluid was similarly defined: improved, an increase of 25% of normal amount; stable, an increase of lecithin was <25%; and deteriorated, a decrease of 25% in normal amount. Effective rate was equal to (number cases of improved/total cases number) × 100%.

Efficacy Evaluation

The efficacy evaluation was conducted according to the criteria established by the "Guidelines for Clinical Research of Traditional Chinese Medicine New Drugs (Trial)" published by the Ministry of Health of the People's Republic of China in 2002[29] which include (1) clinical recovery: the symptom score after treatment decreased by 95% or more than pre-treatment; (2) marked effect: symptom scores after treatment decreased by 60% or more than pre-treatment, but less than 95%; (3) improvement: symptom scores after treatment decreased by 30% or more than pre-treatment, but less than 60%; and (4) failure: symptom score after treatment decreased by 30% or less than pre-treatment. The percentage of change in NIH-CPSI score was calculated at each given follow-up time from baseline as (Post-treatment – baseline) / baseline × 100%.

Adverse Events

We also communicated with each participant weekly by telephone to follow up any adverse event or side effect.

Statistical Analysis

Statistical analysis was performed by SPSS 22.0 for Windows. Statistical significance was defined as $P<0.05$ with a two-tailed test. Measured data,

if normally distributed, are described by mean ± standard deviation ($\bar{x} \pm s$). In the measurement data set, if the data is normally distributed, the paired data *t*-test is used. If the data does not match the normal distribution, the Wilcoxom rank sum test of the paired data is used. Between the two groups, the grade data were analyzed by Ridit analysis. Missing data were not included as the dropped cases had not received all the treatments.

RESULTS

A total of 82 eligible patients was screened and enrolled, 10 were excluded. Of 72 randomly assigned patients, 65 completed the 4-week course of treatment and were assessed at week 4, 34 from MDGP group and 31 from the placebo control group. Baseline characteristics of the patients are presented in Table 1 and flowchart for patients recruitment is shown in Figure 1. Before treatment, there was no difference between the two groups in age, course of disease and NIH-CPSI scores (P>0.05).

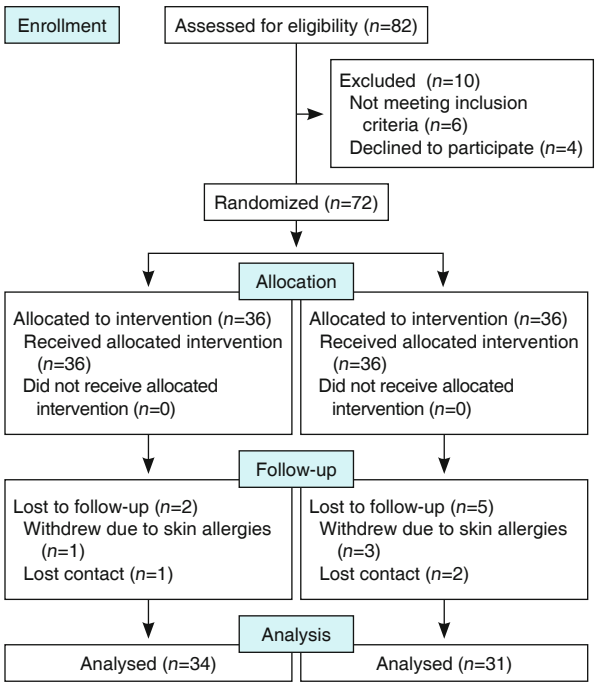

Figure 1. Flow Diagram of Patients with CNP

Primary Outcome

NIH-CPSI total scores of chronic prostatitis improved more signifcantly in MDGP group than placebo control group at week 2 and 4 (P<0.05, Table 2).

Secondary Outcomes

The prostatic fluid analysis was performed before and after treatment among 17 patients in MDGP group and 15 patients in placebo control group who were willing to undergo the examination. The rank sum test analysis showed that there was no significant difference in WBCs and lecithin bodies between the two groups at pre-treatment (P>0.05). The treatment group had higher effective rates in lowing WBCs and lecithin levels than the placebo control group (P<0.05). Both the MDGP and placebo control groups increase lecithin bodies, and there is no significant difference between the two groups (P>0.05, Table 3).

Table 1. Participant Demographic and Baseline Characteristics ($\bar{x} \pm s$)

Characteristics	MDGP (34 cases)	Placebo (31 cases)
Age (years)	31.2 ± 7.2	33.2 ± 7.0
Duration of illness (Month)	30.7 ± 27.5	22.8 ± 24.7
Pain or discomfort (Score)	15.2 ± 7.4	12.6 ± 8.2
Voiding symptoms (Score)	6.6 ± 2.9	6.1 ± 3.1
Symptom severity (Score)	21.7 ± 9.4	18.6 ± 10.4
Quality of life (Score)	9.8 ± 2.3	9.2 ± 2.3
Total scores	31.6 ± 10.6	27.9 ± 11.6

Table 2. NIH-CPSI Scores Between Two Groups ($\bar{x} \pm s$)

Items	Week	MDGP (34 cases)	Placebo (31 cases)
Pain or discomfort	0	15.2 ± 7.4	12.6 ± 8.2
	2	10.0 ± 5.3*	10.7 ± 7.6
	4	7.2 ± 5.5*	9.2 ± 7.8
Urination	0	6.6 ± 2.8	6.1 ± 3.1
	2	5.2 ± 2.4	4.7 ± 3.0
	4	3.8 ± 3.0	4.1 ± 2.9
Symptom severity	0	21.7 ± 9.4	18.6 ± 10.4
	2	15.1 ± 6.8*	15.2 ± 8.2
	4	11.1 ± 7.9*	13.3 ± 9.3
Quality of life	0	9.8 ± 2.3	9.2 ± 2.3
	2	8.5 ± 2.5*	8.9 ± 2.9
	4	6.8 ± 3.0	7.3 ± 3.5
Total scores	0	31.6 ± 10.6	27.9 ± 11.6
	2	23.4 ± 8.5*	23.8 ± 9.5
	4	17.8 ± 10.1*	20.8 ± 11.8

Note: *P<0.05 *vs.* placebo control group at the same time points

Evaluation of Clinical Efficacy

The clinical efficacy was evaluated after 4 weeks treatments in the two groups. The total clinical effective rate was 73.53% (25/34) in the MDGP group, which was significally higher than the placebo control

Chin J Integr Med 2021 Mar;27(3):170-176

Table 3. Comparison of WBC and Lecithin Bodies in the Prostatic Fluids Between Two Groups (Case)

Group	Case	Time	WBC counts					Lecithin body			
			Normal	+	++	+++	++++	0	+	++	+++
MDGP	17	Week 0	1	6	6	1	3	0	9	5	3
		Week 4*	7	5	5	0	0	0	3	6	8
Placebo	15	Week 0	2	2	7	1	3	3	6	4	2
		Week 4	1	6	3	5	0	0	0	8	7

Note: *P<0.05 *vs*. placebo group after treatment on WBC counts

group with 48.39% (25/31, P<0.05).

Assessment for Patients Blinding

Assessment for patients blinding was conducted at week 4. We asked participants to guess which group they believed they had been assigned. Thirty one patients (91.2%) of 34 in the MDGP group and 6 (19.4%) of 31 in the placebo control group guessed their group assignment correctly, 3 patients in the MDGP group and 25 in the placebo control group guessed incorrectly. Chi-square test analysis showed that no statistically significant difference was found between the two groups (P=0.429).

Adverse Events

Totally 4 adverse events (skin allergies) were reported among 72 participants, 1 from MDGP group and 3 in the placebo control group. Analysis showed that there was no difference in adverse effect occurence between the two groups (P= 0.490).

Dropout Rate Analysis

By the end of the trial, the dropout rate was 9.7% (7/72). In the MDGP group, 2 of the 36 patients were lost, 1 declined invitation for treatment due to time and 1 had skin allergies during application. In the placebo control group, 5 of the 36 patients were lost, 2 declined invitation for treatment due to time and 3 had skin allergies during application (Figure 1). Analysis result showed that there was no difference in dropout rate between the two groups (P= 0.290).

DISCUSSION

In this double-blind RCT, a 4-week course of umbilicus treatments with MDGP seems to relieve pain and symptom effectively and increase WBC number in patients with CNP compared with placebo control. A number of scholars have found that placebos have a great effect and drug colour have impact on perceived drug effect.[30,31] In our study, the placebo was brownish in appearance and accompanied by a mint flavor similar to the real Dinggui Powder. The main ingredient is starch and coffee grounds, which do not contain active pharmacological components, but also can play a good staining effect in the placebo. In our trial, blinding was successful partly because all the patients were naïve to umbilicus treatment. Additionally, the appearance and flavor were the same in the placebo and treatment powder.

The basic pathogenesis of CNP in CM is characterized by blood stasis and the general treatment principle is to "remove blood stasis and dredge collaterals".[32] According to ancient CM literature,[33] there are 9 kinds of umbilical therapies. Dinggui Power exerts the effect by warming and dispelling cold, relieving pain and promoting qi circulation to remove meridian obstruction. Studies have shown that the main active ingredient of *Flos Caryophylli* is eugenol. The main active ingredient of *Cortex Cinnamomi* is cinnamaldehyde. Modern pharmacological studies have shown that the main components of *Flos Caryophylli*, *Cortex Cinnamomi* and *Cortex Phollodendri* have good antibacterial, anti-inflammatory and analgesic effects.[34-37] *Clove* can relieve pain and promote transdermal absorption of herbs. *Cortex Cinnamomi* can also promote local blood flow and reduce vascular resistance. The combination of the three herbs relieved local pain and urinary discomfort in patients with chronic prostatitis.[17,38]

Several limitations of the study should be noted. First, the sample size was relatively small to generate statistical significance due to the large variation in symptoms. However, the study tested the feasibility of the trial to enable us to conduct a more large RCT. Second, the treatment duration was relatively short and no further follow-up. In a systematic review, the treatment duration in the 23 RCTs of conventional medications ranged from 4 to 52 weeks, with a median duration of 12 weeks.[39] Third, the placebo powder we used also with a mint

flavor and may also give stimulation on the umbilicus to exert some effect. One participant in MDGP group and 3 participants in placebo control group had skin allergies during treatment. The adverse effects should be carefully investigated further.

Taken together, the external application of modified Dinggui Powder in acupoint CV 8 has obvious therapeutic effect on CNP patients. A 4-week treatment seems to relieve patients' pain and symptom effectively and increase the leukocytes number in patients with CNP.

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Yin J and Huang H received the research funding and led the entire study. Yin J and Zhou MJ participated in the design of the study and performed the statistical analysis. Wang KX, Chao Y, Wang YH, Ji J and Pan W participated in recruitment and overseeing participants medical affairs. Zhao L and Huang H drafted the manuscript. All of the authors have read and approved the final manuscript for publication.

Acknowledgement

We gratefully acknowledge the study participants. Without them, this study would not have been possible.

REFERENCES

1. Suskind AM, Berry SH, Ewing BA, Elliott MN, Suttorp MJ, Clemens JQ. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. J Urol 2013;189:141-145.
2. Krieger JN, Nyberg L Jr, Nickel JC. NIH consensus definition and classification of prostatitis. JAMA 1999;282:236-237.
3. Sahin S, Bicer M, Eren GA, Tas S, Tugcu V, Tasci AI, et al. Acupuncture relieves symptoms in chronic prostatitis/chronic pelvic pain syndrome: a randomized, sham-controlled trial. Prostate Cancer Prostatic Dis 2015;18:249-254.
4. Lee SH, Lee BC. Use of acupuncture as a treatment method for chronic prostatitis/chronic pelvic pain syndromes. Curr Urol Rep 2011;12:288-296.
5. Qin Z, Zang Z, Zhou K, Wu J, Zhou J, Kwong JSW, et al. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: a randomized, sham acupuncture-controlled trial. J Urol 2018;10:513-520.
6. Liu BP, Wang YT, Chen SD. Effect of acupuncture on clinical symptoms and laboratory indicators for chronic prostatitis/chronic pelvic pain syndrome: a systematic review and meta-analysis. Int Urol Nephrol 2016;48:1977-1991.
7. Zhou MJ, Yang MY, Chen L, Yu C, Zhang W, Ji J, et al. The effectiveness of long-needle acupuncture at acupoints BL 30 and BL 35 for CP/CPPS: a randomized controlled pilot study. BMC Compl Altern Med 2017;17:263.
8. Franco JV, Turk T, Jung JH, Xiao YT, Lakhno S, Garrote V, et al. Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome. Cochrane Database Syst Rev 2018;5:CD012551.
9. Han Y, Chen RR, Liu YM, Dai XM, Su SQ. The research for aesthetic evaluation and aesthetic characteristics of Chinese young female. Chin J Aesthetic Med (Chin) 2011;7:1060-1062.
10. Moore Keith L, ed. Before we are born: basic embryology and birth defects. 2nd Edition. Philadelphia: W. B. Saunders Company; 1983:82.
11. Lu QH, Yang HQ, Chen L, Li H, Xie S. Analysis of the skin temperature distribution of infrared thermography of normal youth. Chin J Biomed Enginer (Chin) 2007;4:528-531, 536.
12. Zhou JZ, Wang DR, Zou Y, Xia Q, Pu M, Jiang C, et al. 521 cases of navel measurement in children. J Chron Dis (Chin) 2006;4:77-78.
13. Chen DX. The current situation of peritoneoscopic appendectomy through the umbilicus. Chin J Modern Drug Application (Chin) 2008;2:53.
14. He ZQ, Zhang J, Chen WH, Wang JY, Tang JH, Tang L. New solution to the mechanism of umbilical therapy—meridian fascia. J Pract Med (Chin) 2005;21:2099-2100.
15. Wu J, ed. WU Jie-ping urology. Jinan: Shandong Science and Technology Press; 2004:584-586.
16. Chen R, Nickel JC. Acupuncture ameliorates symptoms in men with chronic prostatitis/chronic pelvic pain syndrome. Urology 2003;61:1156-1159.
17. Zhao B, Wang B, Mo XW, Li HS, Dang J, Li BZ, et al. Dingguisan attached Shenque acupoint and Huiyin acupoint for the treatment of chronic nonbacterial prostatitis. Chin J Human Sex (Chin) 2014;23:59-62.
18. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. J Eval Clin Pract 2004;10:307-312.
19. Liu Z, Yao KY, Wang HR, Li YL, Li ML, Liu JP, et al. Acupoint herbal patching at Shenque (CV 8) as an adjunctive therapy for acute diarrhoea in children: a systematic review and meta-analysis. Eur J Integr Med 2017;10:25-37.
20. Nickel JC, Nyberg LM, Hennenfent M. Research guidelines for chronic prostatitis: consensus report from the first National Institutes of Health International Prostatitis Collaborative Network. Urology 1999;54:229-233.

21. Litwin MS, McNaughton-Collins M, Fowler FJ, Nickel JC, Calhoun EA, Pontari MA, et al. The National Institutes of Health Chronic Prostatitis Symptom Index: development and validation of a new outcome measure. Chronic Prostatitis Collaborative Research Network. J Urol 1999;162:369-375.
22. Nickel JC, Downey J, Hunter D, Clark J. Prevalence of prostatitis-like symptoms in a population based study using the National Institutes of Health Chronic Prostatitis Symptom Index. J Urol 2001;165:842-845.
23. Liang CZ, Hao ZY, Li HJ, Wang ZP, Xing JP, Hu WL, et al. Prevalence of premature ejaculation and its correlation with chronic prostatitis in Chinese men. Urology 2010;76:962-966.
24. Guo J, Zhang YQ, Jia JM, Jiao YZ, Wu YQ, Li WX, et al. The observation of chronic prostatis patients using the National Institutes of Health Chronic Prostatitis Symptom Index. National J Androl 2002;8:127-129.
25. Wang Y, He L, Zhou Z, Jin L, Meng J, Sun G, et al. The association between metabolic syndrome and the National Institutes of Health Chronic Prostatitis Symptom Index: results from 1673 men in China. Urology 2013;82:1103-1107.
26. Huang ZY. The significance of leukocyte count in prostatic fluid of patients with chronic prostatitis. J Med Forum (Chin) 2003;24:20-21.
27. Ying J, Zhou MJ, Chen HY, Chen L, Zhang W, Ji J, et al. Effect of essential oil on patients with chronic prostatitis/chronic pelvic pain syndrome: a pilot randomized controlled trial. Chin J Integr Med 2019;25:91-95.
28. Peng FH, Yang JR, Peng LK, Xie XB, Yang LY, Zhang XZ, et al. The relationship between the positive rate of bacterial culture and the number of purelent cells and lecithin body in prostatic fluid. Chin J Androl (Chin) 2010;24:51-53.
29. Zheng XY, ed. Guiding principle of clinical research on new drugs of traditional Chinese medicine (Trial). Beijing: China Medical Science and Technology Press; 2002:171-172.
30. Zhang WC, Yuan LZ, Lu YQ, Luo J. The history and development of experiment design for placebo effect studies. Adv Psychol Sci (Chin) 2011;19:1115-1125.
31. Tao D, Wang TY, Wang TS, Qu XD. Influence of drug colour on perceived drug effects and efficacy. Ergonomics 2018;61: 284-294.
32. Mo XW, Wang B, Li HS, Dang J, Han L. The scheme and method of traditional Chinese medicine in treating chronic prostatitis. World Chin Med (Chin) 2013;8:1244-1247.
33. Wang ML, Ma YX. The ancient clinical application of umbilical therapy for retention of urine. Chin Acup Moxibust (Chin) 2017;37:185-187.
34. Song YY, Li Y, Zhang HQ. Anti-inflammatory and analgesic activity of Syringin and its possible mechanism. Chin Wild Plant Res (Chin) 2010;29:27-30,41.
35. Li L, Han GZ. Advances in the volatile oils from traditional Chinese medicine as transdermal absorption enhancers. Chin J New Drugs (Chin) 2008;17:914-918,946.
36. Vasconcelos NG, Croda J, Simionatto S. Antibacterial mechanisms of cinnamon and its constituents: a review. Microb Pathogen 2018;120:198-203.
37. Xian YF, Mao QQ, Ip SP, Lin ZX, Che CT. Comparison on the anti-inflammatory effect of *Cortex Phellodendri* Chinensis and *Cortex Phellodendri* Amurensis in 12-O-tetradecanoyl-phorbol-13-acetate-induced ear edema in mice. J Ethnopharmacol 2011;137:1425-1430.
38. Sun S, Zhou H, Li HS, Wang B. Curative effect of Dinggui Powder dressing umbilicus in the treatment of type Ⅲ prostatitis (type of qi stanation and blood stasis) in 58 cases. Chin J Human Sex (Chin) 2014;23:50-52.
39. Anothaisintawee T, Attia J, Nickel JC, Thammakraisorn S, Numthavaj P, McEvoy M, et al. Management of chronic prostatitis/chronic pelvic pain syndrome: a systematic review and network meta-analysis. JAMA 2011;305:78-86.

(Accepted February 27, 2019; First Online April 20, 2020)
Edited by TIAN Lin