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Original Article

Effect of Essential Oil on Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Pilot Randomized Controlled Trial

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ABSTRACT **Objective:** To evaluate the efficacy and safety of essential oil treatment for type Ⅲ chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). **Methods:** A randomized controlled trial was conducted from December 2014 to October 2015. Seventy type Ⅲ CP/CPPS patients were assigned to the essential oil group (35 cases) or almond placebo oil control group (35 cases) by a random number table. The oil was smeared by self-massage on the suprapubic and sacral region once a day for 4 weeks. The National Institutes of Health Chronic Prostatitis Syndrome Index (NIH-CPSI) and expressed prostatic secretions (EPS) were examined. The primary outcome was NIH-CPSI pain domain. The secondary outcomes included other NIH-CPSI domains and laboratory examinations of EPS. Adverse events were also observed. **Results:** Sixty-six subjects completed the full 4-week treatment. There was no significant difference between almond oil control and essential oil groups in terms of the total score of NIH-CPSI, pain, quality of life and urination domain scores of NIH-CPSI and EPS examinations (P>0.05). In the essential oil group, pain between rectum and testicles (perineum) in the domain of pain or discomfort was significantly reduced at week 2 and week 4 compared with almond oil control group (P<0.01). No serious adverse events occurred. **Conclusion:** The essential oil may reduce the pain or discomfort in the perineum region in patients with CP/CPPS. (Registration No. ChiCTR-IPR-14005448)

KEYWORDS essential oil, chronic prostatitis/chronic pelvic pain syndrome, randomized controlled trial

According to the National Institutes of Health (NIH) Consensus Definition and Classification of Prostatitis, there are 4 categories of prostatitis. Type Ⅲ chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), including type ⅢA inflammatory and type ⅢB non-inflammatory,[1] is one of the most common genitourinary diseases among adult males. The prevalence of CP/CPPS is estimated to range from 2% to 10%, and the overall lifetime prevalence from 9% to 16%.[2] Pelvic pain, inflammation of the prostate, voiding symptoms, and sexual disturbance are the most common symptoms of CP/CPPS,[2,3] which significantly decrease the patients' quality of life.

While antibiotics are widely used as first-line mediations, their efficacy for CP/CPPS is disputed.[2,4-7] Studies have shown that there was no significant difference in the number of prostatic bacteria between CP/CPPS and asymptomatic patients.[4] Indeed, bacteria was found in the urinary tract of less than 10% of CP/CPPS patients.[2] As an inflammatory disease, anti-inflammatory medications are commonly used to treat CP/CPPS.[7] However, the effectiveness of these medications for CP/CPPS patients has not yet been rigorously tested by a large-scale randomized control trials (RCTs).[5,6] Moreover, the adverse effects of these medications on elderly patients are of serious concerns.[4,7,8] Given patients' lack of satisfaction with conventional treatments, they are increasingly turning toward alternative therapies.

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Oils containing various Chinese herb extracts are very popular for pain relief in China and Eastern Asia. Sandalwood (lignum santali albi), jasmine, and cinnamon are aromatic herbs that are traditionally used by for regulating qi, removing blood stasis, and relieving pain.[9,10] Previous studies found cinnamon had an antibacterial effect[11] and could prevent carbon tetrachloride-induced damage on the male reproductive system.[12] Rosemary and clary sage are common folk medicines worldwide and have been recognized for their analgesic and antibacterial effects.[12-14] According to the doctrine of Chinese medicine (CM), pain related to CP/CPPS is the result of blockade of dampness-heat, blood stasis, and qi stagnation, or the unnourishing effects of insufficient qi and blood in the body.[15] The objective of this study was to determine whether the essential oil had a greater therapeutic effect for CP/CPPS patients than the placebo oil by reducing the symptoms of chronic prostatitis. The safety and tolerability of the essential oil were also evaluated.

METHODS

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) aged at least 18 years old; (2) diagnosed as type Ⅲ CP/CPPS;[1] and (3) signed written informed consent. Exclusion criteria included: (1) patients with prostate cancer, pelvic radiotherapy, history of transurethral procedures, or urinary tract infection in the past 6 months; (2) a skin allergy, hypertension, cardiovascular diseases, epilepsy, or other unstable medical conditions; (3) had an investigational drug treatment within the past 6 months; or (4) alcoholism or drug abuse within the past year.

Estimation of Sample Size

Sample size estimation based on the pilot study, the essential oil could produce approximately 3.5 point reduction in pain domain of National Institutes of Health (NIH)-Chronic Prostatitis Syndrome Index (CPSI).[16] Thirty subjects per group were needed to yield statistical significance at a power (1-β) of 80% and a two-tailed level of α=0.05, with an estimated standard deviation of 4.7 and a dropout rate of 15%. A total of 70 subjects of 2 groups should be recruited for the study.

Subjects and Grouping

The Longhua Hospital Medical Ethics Committee, Shanghai University of Traditional Chinese Medicine (SUTCM) approved the study protocol (No. 2014LCSY30). The trial was registered on the Chinese Clinical Trial Registry (No. ChiCTR-IPR-14005448). Seventy eligible subjects were recruited from the Outpatients at Longhua Hospital, SUTCM from December 2014 to October 2015 and randomly assigned to the treatment (essential oil, 35 cases) or placebo group (almond oil, 35 cases).

Randomization and Blinding

The random codes were generated using Excel and sealed in opaque envelopes that were labeled with the sequence number by a statistician who was not directly involved in the study. The project coordinator kept the envelopes and when an eligible subject was recruited, an envelope in the sequence was opened and the coordinator recorded the code. The oil with the same code was then assigned to the participant. The assessors were responsible for the outcome assessment and were not aware of the participants' group. Data were doubled entered and locked on the computer after assessment. The statistician analyzed the data without knowing the group identity. The essential and placebo oil had a similar odor and color. In the pilot study, the placebo oil had successful blinding and credibility.

Treatment

The CM doctors directed the subjects to self-administer the essential or placebo oil. In the essential oil group, 10 drops of essential oil (A Drop Water™ essential oil consists of sandalwood, jasmine, ginger, cinnamon, rosemary, clary sage, and other ingredients) were added in 10 mL of almond oil, which is commonly used as a carrier base for essential oil. In the placebo group, 10 drops of almond oil were added in 10 mL of almond oil. Both oils were prepared by the supplier (Golden Eagle Enterprise Group Limited, Hong Kong SAR, China) before the study. The subjects were briefly instructed as follows: 2 mL of diluted oil was smeared evenly on the suprapubic or hypogastric region, Guangyuan (CV 4) and Qihai (CV 6) acupoints and the sacral region [Shangliao (BL 31), Ciliao (BL 32), Zhongliao (BL 33), Xialiao (BL 34) acupoints, called Eight Liao], and followed by a clockwise self-massage for 5 min once per day. The treatments lasted for 4 weeks.

Outcome Assessment

The NIH-CPSI is a questionnaire commonly used for the assessment of symptom severity among men with CP/CPPS. The 13-item questionnaire contains 3 domains to assess the pain, urination, and quality of

life.[16] In each item, score ranges are 0–1 (6 items), 0–3 (2 items), 0–5 (3 items), 0–6 (1 item), and 0–10 (1 item). The pain domain of the NIH-CPSI questionnaire was used to measure primary outcomes of the study which assess the pain or discomfort in the areas. The total scores of NIH-CPSI and other 2 domains (urination and quality of life) in the questionnaire and prostate gland fluid examination were used to measure the secondary outcomes. The NIH-CPSI questionnaire was administered at 0, 2, and 4 weeks. The prostate gland fluid was tested at baseline and completion of the treatment, respectively.

The change in numbers of white blood cells (WBCs) and lecithin bodies in expressed prostatic secretions (EPS) was examined. The normal range of WBC is less 10 /high power field. The clinical efficacy of oil in WBCs was defined as follows: 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. The efficacy of oil in lecithin 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=(number of improved/total number) × 100%.

Adverse Event

Adverse events were measured by the patient self-reporting after treatments, e.g. skin allergy, pain, numbness, or other discomforts. The assessors (licensed CM practitioners) were trained to ensure the consistency and reliability of the assessment.

Statistical Analysis

Statistical analysis was performed by SPSS 22.0 for Windows. Categorical data, including baseline data and efficacy assessment of the prostate gland fluid was examined using the Chi-square (χ^2) test or Fisher's exact test. Continuous baseline data and NIH-CPSI scores were analyzed using one-way analysis of covariance (ANCOVA) with the adjusted covariate. The differences between 2 groups at each time point were further examined using Student's *t*-test. Statistical significance was defined as $P<0.05$ with a two-tailed test.

RESULTS

Participants and Baseline Characteristics

Of 70 enrolled subjects, 66 patients (94.3%) completed the 4-week treatment, 32 in the essential oil group and 34 in the almond oil group. The flowchart of the study is presented in Figure 1. There were no significant intergroup differences in baseline characteristics between 2 groups ($P>0.05$, Table 1).

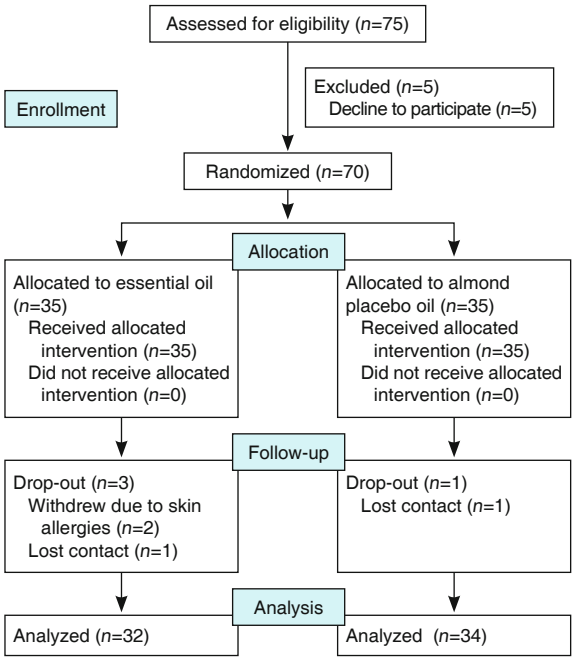

Figure 1. Flowchart of the Study of Essential Oil on CP/CPPS Patients

NIH-CPSI

As shown in Table 2, In the essential oil group, the pain or discomfort between rectum and testicles (perineum) was significantly reduced at week 2 and 4 compared to the almond oil control group, respectively (both $P<0.01$). As shown in Table 3, the essential oil group had a larger reduction in the total score of NIH-CPSI and domain scores including pain or discomfort, quality of life, urination, and impact of symptom at week 2 and week 4. However, there were no statistically significant differences between the 2 groups ($P>0.05$).

Laboratory Examinations

At baseline, 3 subjects in the essential oil group refused the examination of EPS. After the intervention, 1 subjects in placebo group and 3 subjects in the essential oil group refused the EPS examination.

The essential oil group had higher effective rates in WBCs and lecithin levels than the placebo group. However, there was no significant difference between the 2 groups ($P>0.05$, Table 4).

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Table 1. Characteristics of the Subjects

Characteristics	Placebo (35 cases)	Essential oil (35 cases)
Age (Year, $\bar{x} \pm s$)	32.2 ± 8.4	30.9 ± 6.7
Live with spouse [Case (%)]	18 (51.4)	21 (60.0)
Sex frequency per month(Time, $\bar{x} \pm s$)	2.6 ± 1.9	2.5 ± 1.9
Prostatitis history [Case (%)]	15 (42.9)	13 (37.1)
Symptom duration from the onsets (months, $\bar{x} \pm s$)	24.0 ± 26.6	24.6 ± 31.0
Major symptoms[a] [Case (%)]		
Pain or discomfort in lower abdomen, waist, pelvic, perineum, and rectum	19 (54.3)	23 (65.7)
Pain during urination, dysuria, micturition, and turbid urine	20 (57.1)	23 (65.7)
Sexual dysfunction	2 (5.7)	2 (5.7)
WBC (Case)		
Beyond normal range	31	27
In normal range	4	5
Unchecked	0	3
Lecithin body (Case)		
Beyond normal range	25	25
In normal range	10	7
Unchecked	0	3

Notes: [a]Some subjects had more than 1 symptom; WBC, white blood cell

Adverse Events

Two subjects in the essential oil group withdrew from the trial due to skin allergies. No serious adverse events occurred in both groups.

DISCUSSION

This study is a RCT to evaluate the efficacy and safety of a self-administrated essential oil treatment compared to a placebo (almond oil). The pilot study demonstrated that the essential oil significantly reduced the pain or discomfort in the area between the rectum and the perineum for patients with CP/CPPS.

A self-administered essential oil massage is a feasible self-management therapy. Aromatherapy is often used to manage several conditions, including pain, anxiety, agitation, insomnia and stress. In the present study, we demonstrated that an essential oil significantly reduced pain in the rectum and perineum, but not in the testicles, tip of the penis, or the pubic or bladder area compared to the placebo at week 2 and 4. There was no statistically significant difference in the total scores of NIH-CPSI and its domains between these 2 groups. The data suggested the essential oil massage may specifically work on pains in the areas of rectum and perineum.

Several limitations of the study should be noted. First, the sample size was relatively small to generate

Table 2. Pain or Discomfort Domain Scores of NIH-CPSI ($\bar{x} \pm s$)

Group	Case	Time	Pain or discomfort domain						
			1a	1b	1c	1d	2	3	4
Placebo	35	Week 0	1.1 ± 1.4	1.1 ± 1.4	0.8 ± 1.4	1.9 ± 1.6	1.5 ± 1.4	1.3 ± 1.3	3.8 ± 2.4
	34	Week 2[a]	0.1 ± 1.0	–0.4 ± 0.9	–0.2 ± 0.9	–0.6 ± 1.2	–0.2 ± 0.9	–0.4 ± 1.0	–0.7 ± 1.0
	34	Week 4[a]	0.1 ± 0.9	–0.3 ± 1.6	–0.1 ± 1.0	–0.8 ± 1.6	–0.3 ± 0.9	–0.5 ± 1.2	–0.8 ± 1.8
EO	35	Week 0	2.1 ± 1.7	1.1 ± 1.5	0.7 ± 1.2	1.2 ± 1.5	1.7 ± 1.7	1.3 ± 1.8	4.5 ± 2.5
	34	Week 2[a]	–0.6 ± 0.9*	–0.3 ± 0.5	0.1 ± 0.6	–0.2 ± 1.1	–0.3 ± 0.8	–0.4 ± 1.1	–0.8 ± 1.1
	32	Week 4[a]	–0.6 ± 1.1*	–0.4 ± 2.0	–0.1 ± 1.0	–0.3 ± 1.5	–0.5 ± 1.1	–0.3 ± 1.1	–0.9 ± 1.4

Notes: EO: essential oil; NIH-CPSI: National Institutes of Health Chronic Prostatitis Syndrome Index; 1a: area between rectum and testicles (perineum); 1b: testicles; 1c: tip of the penis (not related to urination); 1d: pain below waist, in the pubic or bladder area; 2. pain or burning during urination over the last week; 3. pain or discomfort during or after sexual climax (ejaculation) over the last week; 4. numeric score of average pain or discomfort over the last week; [a]the changes from week 0; *P<0.01, *vs*. placebo group at the same time

Table 3. Total and Domain Scores of NIH-CPSI ($\bar{x} \pm s$)

Group	Case	Time	Pain or discomfort	Quality of life	Urination	Total score
Placebo	35	Week 0	11.5 ± 7.4	8.5 ± 2.9	4.8 ± 3.1	24.8 ± 10.8
	34	Week 2[a]	–2.4 ± 3.3	–0.6 ± 1.5	–0.5 ± 2.2	–3.6 ± 5.6
	34	Week 4[a]	–2.7 ± 4.9	–0.9 ± 2.1	–1.1 ± 2.6	–4.7 ± 7.3
EO	35	Week 0	12.6 ± 7.3	9.6 ± 2.2	5.5 ± 2.9	27.7 ± 9.8
	34	Week 2[a]	–2.3 ± 3.2	–0.8 ± 1.4	–1.0 ± 1.5	–4.0 ± 4.6
	32	Week 4[a]	–3.2 ± 4.6	–1.5 ± 2.0	–1.6 ± 2.1	–6.4 ± 7.3

Notes: EO: essential oil; NIH-CPSI: National Institutes of Health Chronic Prostatitis Syndrome Index; [a]the changes from week 0

Table 4. Clinical Effectiveness in WBCs and Lecithin Body in the Expressed Prostatic Secretions [Case (%)]

Group	Case	WBCs			Lecithin body		
		Improved	Stable	Deteriorated	Improved	Stable	Deteriorated
Placebo	33	13 (39.4)	10 (30.3)	10 (30.3)	12 (36.4)	16 (48.5)	5 (15.2)
Essential oil	32	15 (46.9)	12 (37.5)	5 (15.6)	13 (40.6)	15 (46.9)	4 (12.5)

Note: EO: essential oil

statistical significance due to the large variation in symptoms. From the preliminary data in the study, if we assume that the reduction in the score of the NIH pain or discomfort domain in the essential oil and placebo group was -3.2 ± 4.6 *vs*. -2.7 ± 4.9, respectively, the effect size was 0.354. Thus, to achieve significance between the essential oil and placebo group with $\alpha = 0.05$, $\beta = 0.2$ in a two-tailed test, 127 patients would be required in each group. However, the study tested the feasibility of the trial to enable us to conduct a large RCT. Second, the treatment duration was too short to accumulate a therapeutic effect. 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.[17] Longer treatment (more than 4 weeks) with essential oil may yield a significant effect. Third, the study did not measure the compliance of the self-administration treatment by the patients. Low compliance with the treatment may lead to a failure to detect the efficacy of the oil. Two subjects had skin allergies during application of the essential oil. The adverse effects should be carefully investigated further.

In conclusion, this pilot RCT confirmed the feasibility of the study. It demonstrated that essential oil treatment may reduce pain and discomfort in the perineum region for patients with CP/CPPS, but its efficacy in reducing CP/CPPS was undetermined. The preliminary findings thus warrant a large-scale controlled trial.

Conflict of Interest

The Golden Eagle Enterprise Group Limited, Hong Kong supported the study.

Author Contributions

Zhang ZJ supervised the study and analyzed the data. Ying J, Zhou MJ, Chen L, Zhang W, Ji J, and Chao Y recruited, educated, assessed the subjects, and collected the data. Ying J and Zhang ZJ designed the study. Chen HY drafted the manuscript. All the authors contributed to the manuscript and approved the submitted version.

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