Effect of a comprehensive therapy plus Gushenyutai plaster administered at Guanyuan (CV 4) on male infertility associated with semen non-liquefaction

Shaofang Peng, Yanping Zheng, Kangzhuang Zheng, Ke Lin, Juhong Wu, Wenqin Zheng, Yongzhong Li, Yang Li, Chuangjian Lin

OBJECTIVE: To observe the clinical effect of Gushenyutai plaster administered at the Guanyuan (CV 4) acupoint on male infertility associated with semen non-liquefaction.

METHODS: Sixty-two male patients with infertility caused by semen non-liquefaction were randomized into a treatment and control group. The control group received comprehensive therapy, which included oral administration of clarithromycin sustained release tablets, hip bath with Zhongyaoxi-aoyan granules, prostate massage, and transurethral microwave treatment. The treatment group was administered Gushenyutai plaster in addition to the comprehensive therapy. Both groups were treated for 8 weeks. After treatment, the clinical effect and pregnancy rate were assessed and compared between the two groups.

RESULTS: The effective rate of the treatment group was significantly higher than that of the control group (96.77% vs 70.97%, P < 0.05) and the pregnancy rates of the treatment group and control groups were 38.71% and 16.13%, respectively (P < 0.05).

CONCLUSION: The effect of Gushenyutai plaster plus comprehensive therapy was better than that of the comprehensive therapy alone on male infertility induced by semen non-liquefaction.

INTRODUCTION
Abnormal sperm liquefaction occurs when sperm do not begin to liquefy after more than 1 h, or do not completely liquefy 30 min after ejaculation. While these conditions are respectively referred to as delayed

© 2014 JTCM. All rights reserved.

Key words: Infertility, male; Treatment outcome; Point CV 4 (Guanyuan); Semen non-liquefaction; Gushenyutai plaster

JTCM | www.journaltcm.com 666 December 15, 2014 | Volume 34 | Issue 6 |
Materials and Methods

Subjects
Sixty-two male patients with infertility caused by semen non-liquefaction were recruited from the infertility clinic of Shantou Traditional Chinese Medicine Hospital from July 2007 to October 2011. After obtaining informed consent from the patients, 62 random numbers were chosen from a random number table. Odd numbers were assigned to the treatment group, while even numbers and zero were assigned to the control group. Cards were filled out for each patient after equalizing the number of patients in each group. Cards were placed into sealed opaque envelopes and each envelope was numbered. The envelopes were retained by a specially appointed person and were distributed after the patients met the inclusion criteria.

Patient data
The treatment group (n=31) age ranged from 22 to 36 years old (average 26.3) with a disease course of 1 to 9 years (average 3.2). In the treatment group, there were 21 primary infertility cases and 10 secondary infertility cases. The control group (n=31) age ranged from 22 to 35 years old (average 25.6) with a disease course of 1 to 8 years (average 3.0). In the control group, there were 19 primary infertility cases and 12 secondary infertility cases. There was no statistical difference in age, medical history, disease course, or difference in sterility type between the two groups (P>0.05).

Inclusion criteria
To be included in the study, patients must have had a normal sexual history after marriage for at least 1 year. Patients were included if, after ejaculation, sperm did not liquefy after 60 min or contained a non-liquefied clot at room temperature. According to the World Health Organization recommended methods, non-liquefaction was tested by semen collection via masturbation after 3 to 7 days of abstinence.

Exclusion criteria
Patients were excluded from the study if they had aspermia or oligospermia. Patients could not have reproductive endocrine abnormalities caused by the testicles or various urogenital infections such as ureaplasma urealyticum and chlamydia trachomatis. Patients with prostatic hyperplasia and prostatic tumors that significantly affect the first diagnosis and treatment were also excluded, as were patients with mental disorders.

Treatment
The control group received prostate massage, transurethral microwave treatment, Zhongyaoxiaoyan granules, and clarithromycin slow-release tablets. Prostate massage was performed once every 3 to 4 days, twice a week. Transurethral prostate microwave treatment was performed with a CYP 1 microwave therapy apparatus (Zhuhai Hokai Medical Instruments Co., Zhuhai, China) at 15 W for 15 min, twice a week. Zhongyaoxiaoyan granules (Shenzhen China Resources 999 Modern Chinese Medicine Co., Ltd., Shenzhen, China) were administered every night. Put the granules and boiling water at a dilution of 1:120 to a basin, and after cooling...
ing the water to 42°C, a hip bath was given for 30 min. Hot water was added occasionally to maintain the temperature. Clarithromycin slow-release tablets (Guangzhou Cypress Production Rose Pharmaceutical Co., Ltd., Guangzhou, China), 0.5 grams, were given once a day for 4 weeks as a course. Patients were observed for 8 weeks. The treatment group received the same therapy as that of the control group with additional Gushenyutai plaster (Shenzhen China Resources 999 Modern Chinese Medicine Co., Ltd., Shenzhen, China) administered at the Guanyuan (CV4) acupoint, twice a day, for 30 min each time. Gushenyutai plaster is made from 23 herbs including: Tusizi (Semen Cucurbitae), Chuanxuduan (Radic Dipaci Asperoidis), Sangjisheng (Herba Taxilli Chinensis), Gouqizi (Fructus Lycii), Baishao (Radix Peoniae Alba), Shudihuang (Radix Rehmanniae Praeparata), Shanzhuyu (Semen Cuscutae), Zonglu (Radix Rehmanniae), Sharen (Radix Aucklandiae), Shanyao (Rhizoma Atractylodis Macrocephalae), Huangqi (Radix Astragali Mongolici), Baixao (Herba Taxilli Chinensis), Zisuye (Fructus Psoraleae), Buguzhi (Herba Ecliptae prostratae), Muxiang (Fructus Amomi), Daizix Dipsaci Asperoidis, Petiolus Trachycarpi Fortunei, Legum Aegle Marmelosii, Zhiqiao (Rhizoma Cibotii), Gouteng (Radix Glycyrrhiza uralensis), and stir-frying to scorch Aiye (Herba Ecliptae prostratae) and stir-frying to scorch Zonglu (Petiolaris Trachycarpi Fortunei), and stir-frying to scorch Aye (Folium Artemisiae Argyi). Gouji (Rhozoma Cibotii), Buguzhi (Fructus Poriae), Zisuye (Foli- um Perillae Argutae), Muxiang (Radix Aucklandiae), Mohanlian (Herba Ecliptae prostratae), Huangqin (Radix Scutellariae Baicalensis), Gouteng (Ramulus Uncariae Rhynchophyllae cum Unci), Gancao (Radix Glycyrrhi- zae).

**Effect measurement**

According to the "WHO Library Manual for the Examination and Processing of Human Semen (fourth edition)" and "Guideline of Chinese Traditional Medicine and New Medicine Clinical Research," therapeutic effect was ranked as: recovered, markedly effective, effective, or ineffective. The patient was considered recovered if the liquefaction time was less than 60 min, and the spouses were able to conceive. Markedly effective was reported if spouses were not pregnant within 8 weeks, but the semen completely liquefied in 60 min. Effective was reported when spouses were not pregnant within 8 weeks, and semen incompletely liquefied in 60 min. Ineffective was reported when no obvious changes from before to after treatment were observed.

**Statistical analysis**

The data were processed with SPSS 13.0 (Chicago, IL, USA). Differences in effective rate, pregnancy rate, density, and sperm activity were compared between the two groups by χ² test and t-test. Differences were considered statistically significant when P<0.05.

**RESULTS**

**Curative effect**

This study was designed as a randomized, controlled trail (Figure 1). In the treatment group, 12 cases recovered, eight were markedly effective, 10 were effective, and one was ineffective. The pregnancy rate was 38.71%, and the total effective rate was 96.77%. In the control group, five cases recovered, nine were markedly effective, eight were effective, and nine were ineffective. The pregnancy rate was 16.13%, and the total effective rate was 70.97%. The total effective rate (P<0.05) and pregnancy rate (P<0.05) in the treatment group were significantly higher than those in the control group (Table 1).

**Sperm density**

The sperm density in the two groups was increased after treatment (P<0.01). However, there was no significant difference in the increase in sperm density between the treatment and control groups (P>0.05). After treatment, the percentage of grades a and a+b sperms in both groups increased (P<0.05). The increase in grades a and a+b sperms in the treatment group was significantly higher than that in the control group (P<0.05, Table 2).

**DISCUSSION**

**Pathogenesis of semen non-liquefaction in Chinese and Western Medicine**

Semen non-liquefaction is one of the most common causes of male infertility, and prostate disease is the leading cause of semen non-liquefaction. At present, the pathogenesis of semen non-liquefaction is unclear. It is generally believed that semen liquefaction and solidification are influenced by semenogelin, which is mainly found in the seminal vesicles, and by liquefaction factor, which is found in the prostate. Some known causes of semen non-liquefaction or delayed liquefaction include decreased activity of enzymes during reduced prostatic secretion. Particularly, decreased protease secretion is important because proteases hydrolyze proteins during the semen liquefaction process. Further causes of semen non-liquefaction include increased levels of semenogelin, which disturbs the balance of liquefaction and solidification factors. In addition, seminal vesiculitis, a lack of trace elements (e.g. magnesium, zinc), and congenital deficiencies of the prostate can also cause poor semen liquefaction.

In TCM, there are no specific records on semen non-liquefaction, but there is reference to "stranguria with turbid urine," "sperm thick," "sperm cold," and "sperm hot." Some semen non-liquefaction, according to TCM, mostly results from disordered liver, spleen, and kidney, of which the kidney plays the most important role. Kidney-Yin deficiency and liver-Yang hyperactivity burn the body fluid and cause thick and unliquefied semen. A deficiency in kidney-Yang cannot warm the essence and Qi, leading to semen solidification and non-liquefaction. On the other hand, the kidney is the material basis for development, because the essenc-
Search the interrelated papers to design and determine the clinical program.

Select 62 patients whose seeing a doctor at Shantou hospital of TCM infertility department outpatient service during from July, 2007 to October, 2011, which met the inclusion criteria.

Divided the patients into the treated group with 31 cases and the control group with 31 cases stochastically.

The control group was given comprehensive therapy, which contained oral of Clarithromycin Sustained Release Tablets, hip bath with Zhongyaoxiaoyan granules, prostate massage and microwave treatment.

The treated group was given comprehensive therapy combined with Guanyuan (CV 4) pasted with Gushenyutai Plaster.

Outpatient follow-up treatment after 8 weeks to assess the efficacy by the clinical standards and establish a database.

Figure 1 Flow diagram of the trial

Table 1 Clinical curative effect (n (%))

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Recovered</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>31</td>
<td>12 (38.71)</td>
<td>8 (25.80)</td>
<td>10 (32.26)</td>
<td>1 (3.23)</td>
<td>30 (96.77)</td>
</tr>
<tr>
<td>Control</td>
<td>31</td>
<td>5 (16.13)</td>
<td>9 (29.03)</td>
<td>8 (25.81)</td>
<td>9 (29.03)</td>
<td>22 (70.97)</td>
</tr>
</tbody>
</table>

Notes: the control group was treated with a Zhongyaoxiaoyan granule hip bath, prostate massage and prostate microwave treatment, and clarithromycin slow-release tablets. The treatment group was given the same therapy plus Gushenyutai plaster administered at the Guanyuan (CV 4) acupoint. *P<0.01, compared with the control group.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Treatment</th>
<th>Sperm density ($10^6$/m)</th>
<th>Sperm activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>21.9±17.6</td>
<td>a grade sperm (%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>31</td>
<td>After</td>
<td>71.2±31.0</td>
<td>2.4±1.0'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>df</td>
<td>46.5±25.2</td>
<td>23.3±8.5'</td>
</tr>
<tr>
<td>Control</td>
<td>31</td>
<td>Before</td>
<td>20.8±18.6</td>
<td>5.7±9.0'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After</td>
<td>55.1±13.3</td>
<td>9.4±8.7'</td>
</tr>
<tr>
<td></td>
<td></td>
<td>df</td>
<td>38.0±16.2</td>
<td>44.4±13.7'</td>
</tr>
</tbody>
</table>

Notes: the control group was treated with a Zhongyaoxiaoyan granule hip bath, prostate massage and prostate microwave treatment, and clarithromycin slow-release tablets. The treatment group received the same treatment plus Gushenyutai plaster administered at the Guanyuan (CV 4) acupoint. *P<0.01, compared with the datum before treatment; 'P<0.05, ′P<0.01, compared with the control group.
Comprehensive therapy combined with Gushenyutai plaster is effective for male infertility caused by semen non-liquefaction

Comprehensive therapy, which includes prostate microwave therapy, prostate massage, and Chinese and Western Medicines, is an effective treatment for semen non-liquefaction. Microwave therapy causes local prostate vasodilatation, increased blood flow, increased cellular metabolism, improved phagocyte function, absorption of inflammatory mediators, and promotion of metabolite excretion via increased heat conduction. Prostate massage soothes the prostatic ducts to discharge inflammatory secretions, cellular debris, and bacteria. This effect is beneficial to prostate fluid drainage, circulation improvement. Prostate microwave and massage can heal disrupted tissues and gradually restore normal metabolism of the diseased prostate. 6

Clarithromycin is a large-ring lactone antibiotic, 7 which has low toxicity, high stability in acidic environments, a wide antimicrobial spectrum and strong antibacterial effect, good oral absorption and high bioavailability, a long half-life, and the ability to reach the prostate. Clarithromycin functions by blocking the connection of the nuclear protein 50s subunit, which inhibits protein synthesis in bacteria. Therefore it is an ideal antibiotic, and is often used during the treatment of semen non-liquefaction.

According to TCM, Zhongyaoxiaoyan granules clear heat and detoxify, which promotes blood stasis. Zhongyaoxiaoyan granules are made up of 11 herbs including: Danshen (Radix Salviae Miltiorrhizae), Pugongying (Herba Taraxaci Mongolici), Huanglian (Rhizoma Coptidis), Taoren (Semen Paeonii), Chuanlianzi (Fructus Toosendan), Baijiangcao (Herba Patriniae Scabiosaefoliae), Yuxingcao (Herba Houttyniae cordatae), Madongqing (Radix Ilicis Pubescentis), Mudanpi (Cortex Moutan Radicis), Dingxiang (Flo Syzygii Aromatici), and Guizhi (Ramulus Cinnamomi). The pathological features of chronic prostatitis are inflammatory cell infiltration, epithelial cell blockage, interstitial edema, and gland ductal obstruction. Therefore, inflammation and chronic glandular congestion cause pathological changes, which lead to difficulty in treatment. 8 Infiltration of inflammatory cells, hyperplasia, and degeneration of fibrous tissue cause vein blood stasis. 9 Therefore, Madongqing (Radix Ilicis Pubescentis), Baijiangcao (Herba Patriniae Scabiosaefoliae), and Yuxingcao (Herba Houttyniae cordatae) are used, which clear heat and detoxify, which promotes blood stasis, along with Taoren (Semen Paeonii) and Honghua (Flo Carthami). Modern pharmacological research shows that Madongqing (Radix Ilicis Pubescentis) can promote blood stasis and act as an anti-septic and anti-inflammatory, and its decoction is extremely effective against Staphylococcus aureus. 10 Yuxingcao (Herba Houttyniae cordatae) can promote white blood cell phagocytosis, act as an analgesic and hemostatic, control secretions, and promote tissue regeneration. 11 Baijiangcao (Herba Patriniae Scabiosaefoliae) contains flavonoids that have significant anti-inflammatory activity. In addition, Taoren (Semen Paeonii) extracts have strong anti-inflammatory effects. Benzoylpaeoniflorin from the Mudanpi (Cortex Moutan Radicis) methanol extract can inhibit fibrous protein enzyme and fibrous protein enzyme activity. Dingxiang (Flo Syzygii Aromatici) can inhibit a variety of bacillus, S. aureus, and hemolytic streptococcus bacteria. 12

Research indicates that Zhongyaoxiaoyan granules have good broad-spectrum bacteriostasis and anti-inflammatory functions, can promote blood stasis and increase local blood circulation, and are therefore suitable for hip bath. 13 The treatment is administered after the granules are brewed with boiling water and added to a bath at 42°C (higher temperatures can cause declined testicular sperm production). During the hip bath, compounds from the Zhongyaoxiaoyan granule decocition diffuse into the body through the skin, mucous membranes, sweat glands, hair follicles, corneous layer, and cells. A warm hip bath can expand local blood vessels, increase local blood circulation, and accelerate metabolism. Further, different drugs absorbed through the skin play roles inside the body, such as heat-clearing and detoxifying. They can also warm and activate meridians to adjust imbalances in Yin and Yang, alleviate the symptoms of prostatitis, and accelerate blood circulation in the prostate.

Sixty-two patients with semen non-liquefaction were recruited in our study, and randomly divided into two groups for an 8-week treatment. The results showed that Guanyuan pasted with Gushenyutai plaster in addition to comprehensive therapy had a good curative effect, and was more effective than the comprehensive therapy alone. After treatment, a and a+b grade sperms in both groups were increased (P<0.01), but the increase in the treatment group was significantly better than that in the control group (P<0.01).

Therefore, Gushenyutai plaster is used to reinforce the kidney, strengthen the spleen, and regulate liver. In the formula, Tusizi (Semen Cuscutae), Chuanxuduan (Radix Diplaci Asperoidis), Sangjiseng (Herba Taxilli Chinensis), Gouqizi (Fructus Lycii), Baishao (Radix Paeoniae Alba), Mohanlian (Herba Ecliptae prostratae), Zhumagen (Rhizoma et Radix Boehmeriae), stir-frying to scorch Zonglu (Petiolum Trachycarpus Fortunei), and stir-frying to scorch Aiye (Folium Artemisiae Argyi), and Shanzhuyu (Fructus Corni) nourish the liver and kidney, enrich the essence and blood, and relieve the liver, along with Buguzhi (Fructus Poriae), Gouqizi (Fructus Lycii), and Aiyetan (Folium Artemisiae Argyi), and stir-frying to scorch Zonglu (Petiolum Trachycarpus Fortunei). The combined action of Baizhu (Rhizoma Atractylodis Macrocephalae), Huangqi (Radix Astragali Mongolici), Dangshen (Radix Codonopsis), Shanyao (Rhizoma Dioscoreae)
Gushenyutai plaster works via the Guanyuan (CV 4) acupoint. Acupoint stimulation can dredge meridians, regulate Qi and blood, coordinate Yin and Yang, and promote pathogenic resistance. Additionally, herbs can exert pharmacological effects via skin absorption, which further explains the effects of herbal pastes on acupoints. Guanyuan is adjacent to the prostate, and can locally deliver herbal compounds through the perineum. Moreover, the compounds can affect the Qugu (CV 2), Zhongji (CV 3), Qihai (CV 6), and Changqiang (GV 1) acupoints and meridians and their corresponding Zang-Fu to regulate the liver, spleen, and kidney. The bioavailability of acupoint drugs is higher than that of general oral administration because of the sensitivity and amplification effect of the acupoints on the drugs. Drug administration stimulates the skin and causes expansion of blood vessels, which speeds up blood and lymph circulation, promotes metabolism, and improves local tissue nutrition and immune function. Research shows that acupoint stimulation can prevent and treat disease by diminishing inflammation, improving blood flow, and improving the body’s immune ability. The spleen, kidney, Qi, and blood are the foundation of the human body. Adjustment of immune function can be realized with Chinese medicine, such as by reinforcing the kidney, strengthening the spleen, and promoting blood circulation. Chinese medicine can adjust the prostate zinc level, enhance phagocytosis, and promote the transformation of lymphocytes. Clinical studies have shown that Chinese medicine can significantly reduce abnormally increased immune globulin in the prostatic fluid of CP patients and boost tumor necrosis factor expression. In conclusion, Gushenyutai plaster plus comprehensive therapy was better than that of comprehensive therapy used alone on male infertility induced by semen non-liquefaction.


